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ENERGY EXPENDITURE IN CRITICALLY ILL PATIENTS

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DEANNA L. SWINAMER

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER IN SCIENCE
IN EXPERIMENTAL MEDICINE
DEPARTMENT OF MEDICINE

EDMONTON, ALBERTA
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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled "Energy Expenditure in Critically Ill Patients" submitted by Deanna L. Swinamer in partial fulfilment of the requirements for the degree of Master of Science in Experimental Medicine.

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To my father and mother with
love and appreciation

ABSTRACT

Recently, portable automated systems have become available that are capable of indirectly determining energy expenditure (EE) by gas exchange measurements, in mechanically ventilated critically ill patients. The ability to measure EE in these patients on an individual basis is extremely important. Not only will it help to ensure that appropriate daily caloric intake is achieved but it can also to be used as an assessment tool in research protocols designed to study the efficacy of nutritional support in critically ill patients.

An automated portable system, the Gould 9000IV Computerized Pulmonary Function Cart (Medical Products Division, Dayton, Ohio) was validated using an in vitro system (Chapter 1). Oxygen consumption ($\dot{V}0_2$) and carbon dioxide production ($\dot{V}C0_2$) were simulated using nitrogen and carbon dioxide dilution techniques. Combinations of frequency, tidal volume, minute ventilation and inspired oxygen fraction (F_I0_2) were used to simulate conditions commonly employed in mechanically ventilated critically ill patients. Variations in frequency, tidal volume and minute ventilation had no significant effect on measured $\dot{V}0_2$ and $\dot{V}C0_2$. However, F_I0_2 had a dramatic effect on the accuracy of $\dot{V}0_2$. Errors in measured $\dot{V}0_2$ were 2.6%, 3.5%, 5.9% and 16.9% at F_I0_2 levels of 0.22, 0.40, 0.60 and 0.80, respectively. Addition of a dead space to the spirometer dump port (to prevent room air contamination) markedly reduced a larger error initially found. The accuracy of $\dot{V}C0_2$ was 2.6%. These results support the conclusion that the Gould 9000IV

with the dead space adaptation is capable of accurately measuring $\dot{V}O_2$ and $\dot{V}CO_2$ in mechanically ventilated patients receiving an F_IO_2 of 0.60 or less.

Twenty four hour EE was studied in 10 mechanically ventilated critically ill patients (Chapter 3) to determine: an appropriate factor above the measured resting EE level to account for daily ICU activities; the rise in EE above resting EE that is associated with activities and their contribution to total EE; and the degree to which resting EE exceeds predicted EE (based on the Harris and Benedict equation) and relate the degree of increase to severity of illness of the patient as assessed by the APACHE II score. The validated Gould 9000IV was used to determine continuous EE measurements for patients during the 24 hours studied. Predicted EE was 1501±202 kcal/day (mean±SD) and measured EE was 2186±343 kcal/day which represented a significant increase above predicted EE (47±22%, $p<0.01$). Patients' admission APACHE II score was significantly correlated to the degree to which measured resting EE exceeded predicted EE ($r=0.64$, $p<0.02$).

Activities such as repositioning the patient in bed, patient weighing on a sling-type bed scale, chest physiotherapy and chest x-ray were associated with increases in EE above resting level of 31%, 36%, 20% and 16%, respectively. However, due to their short durations, the contribution of these activities to total EE was small. Total EE was 2342±371 kcal/day or 6.9±2.6% above resting EE (range = 1.4 to 10.6%). An interesting observation made during the 24 hour EE studies was that the administration of analgesia and/or sedation to patients was often associated with a decrease in EE.

Results of 24 hour EE studies in mechanically ventilated critically ill patients support the following conclusions. Severity of illness appears to be related to the large degree of hypermetabolism observed. Routine activites performed on patients result in large increases in EE above measured resting levels. However, because of their short durations, contribution of these activities to total EE was small. An activity factor of not greater than 10% is appropriate to add to resting EE measurements in individual patients to accurately determine daily EE in mechanically ventilated critically ill patients.

The observation that routine administration of analgesia and/or sedation was associated with decreased EE suggested that this may be an important variable that is over-looked when EE measurements are made in critically ill patients. The primary purpose of the study described in Chapter 4 was to determine if routine IV administration of morphine would significantly influence EE in critically ill patients during rest and ICU activites. Additional objectives were to: (1) determine if method of administration, bolus IV injections or continuous IV infusion, would affect EE differently and (2) determine the degree to which measured resting EE exceeded predicted EE (based on the Harris and Benedict equation) when morphine was not administered (period 1) and when morphine was administered to patients (period 2) and relate this to the severity of illness as assessed by the patients' APACHE II score.

Seven mechanically ventilated critically ill patients with a mean APACHE II score of 20±4 were studied. Measurements of EE were

made continuously during a defined sequence of rest, activities and post-activity periods when morphine was not given (period 1) and again when IV morphine was administered at a rate of 0.10 mg/kg/hr as either bolus IV injections or continous IV infusion (period 2).

Predicted EE was 1604±247 kcal/day and measured resting EE was 2220±563 kcal/day during period 1 and 2067±538 kcal/day during period 2. This represented a significant increase in resting EE of 37±17% and 28±17% above predicted EE for periods 1 and 2 respectively ($p<0.01$). Resting EE during period 1 (no morphine) was significantly higher than resting EE during period 2 (during IV morphine administration) ($p<0.01$). No significant correlation was found between the patients' admission APACHE II score and either the degree to which resting EE exceeded predicted EE for period 1 ($r=0.59$, $p=0.08$) or the degree to which resting EE exceeded predicted EE for period 2 ($r=-0.50$, $p=0.13$).

The rise in EE above resting levels associated with the activities of chest x-ray and chest physiotherapy during period 1 were 16±9% and 20±11% and during period 2 were 21±14% and 23±12%, respectively. The difference between periods 1 and 2 was not significant for either activity ($p<0.05$). Total EE (rest + activities measured over a period of 200 minutes) was 315±77 kcal during period 1 (no morphine) and 290±77 kcal for period 2 (during IV morphine administration). This represented a significant reduction in total EE of 9±10% from period 1 to 2 ($p<0.01$). Bolus IV morphine injections and continous IV morphine infusion appeared to have a similiar effect of both resting EE and EE associated with various activities.

The results from this study support the following conclusions. No significant relationship existed between the severity of illness (as assessed by the patients' APACHE II scores) and the degree to which resting EE exceeded predicted EE for periods 1 and 2. Morphine administration at a dose of 0.10mg/kg/hr did not alter the increase in EE above resting levels associated with activities of chest x-ray and chest physiotherapy. Most importantly, routine IV administration of morphine resulted in a significant decrease in resting EE and total EE in mechanically ventilated critically ill patients.

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LIST OF ABBREVIATIONS

APACHE	Acute physiological and chronic
ARDS	Adult respiratory distress syndrome
BTPS	Body temperature, barometric pressure and saturated with water vapor
$C0_2$	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
D	Deceased
EE	Energy expenditure
f	Respiratory frequency
F	Female
F_IC0_2	Inspired fraction of carbon dioxide
F_EC0_2	Expired fraction of carbon dioxide
F_IN_2	Inspired fraction of nitrogen
F_EN_2	Expired fraction of nitrogen
F_I0_2	Inspired fraction of oxygen
F_E0_2	Expired fraction of oxygen
GI	Gastrointestional
H_20	Water
Ht	Height
hr	Hour
ICU	Intensive Care Unit
IV	Intravenous
kcal	calories
Kg	Kilogram

L	Liter
m^2	Square meter
ml	Milliliter
M	Male
MI	Myocardial infarction
MVA	Motor vehicle accident
ND	Not determined
O_2	Oxygen
PSI	Pounds per square inch
PvO_2	Mixed venous oxygen partial pressure
RF	Renal failure
RQ	Respiratory quotient
S	Survived
STPD	Standard temperature and pressure, dry
TBSA	Total body surface area
TISS	Therapeutic intervention scoring system
$\dot{V}_E$	Expired minute ventilation
$\dot{V}_I$	Inspired minute ventilation
V_T	Tidal volume
$\dot{V}CO_2$	Carbon dioxide production
$\dot{V}O_2$	Oxygen consumption
Wt	Weight

CHAPTER 1

OVERVIEW OF ENERGY METABOLISM IN MAN

I Introduction

The question of whether or not provision of nutritional support to mechanically ventilated critically ill patients will improve patient outcome has never been directly addressed. A few retrospective studies have reported reduced morbidity and mortality in this group of patients when they have been fed (17,32,69). However, no prospective randomized controlled clinical trials have been performed to investigate the efficacy of nutritional support in mechanically ventilated critically ill patients. Despite this lack of evidence nutritional support has become routine practice in the management of these patients during the last twenty years.

The evidence to support feeding critically ill patients has largely been extrapolated from other types of patient populations. Pre and postoperative nutritional support of surgical and medical patients has been shown to improved traditional parameters used to assess nutritional status (101,105), reduce morbidity and mortality (24,83,112) and reduce the length of hospital stay (5,24). It has therefore been assumed that prevention of malnutrition and improvement of clinical outcome can be achieved by providing nutritional support to critically ill patients. However, it is unlikely that malnutrition resulting from inability to eat or malabsorption such as seen in many surgical and medical conditions evolves in the same manner as the nutritional state that evolves during concomitant hypermetabolism and hypercatabolism seen in critical illness. Therefore it is also unlikely that the merits of nutritional support can be assumed to apply to critically ill patients until scientifically proven.

In order to justify nutritional support of critically ill patients, prospective randomized controlled clinical trials designed to investigate the effects of feeding versus no feeding need to be performed. Traditional parameters such as anthropometric measurements, liver transport proteins and immunocompetency which are commonly used to indirectly evaluate nutritional status in hospitalized patients, have been shown to be of limited value in assessment of nutritional support of critically ill patients (103).

In the past, the amount of daily nutritional support a critically ill patient would receive has been based on assumed knowledge of energy expenditure (EE). Most often daily energy requirements are derived from various predictive formulas of normal basal metabolism with the addition of arbitrary factors to account for activity and stress of a particular illness. Only recently with advanced technology have portable automated systems become available that are capable of measuring EE in mechanically ventilated patients. Several recent studies have reported that measured EE is extremely variable among critically ill patients and that predictive formulas are inaccurate in assessing EE (7,78,99,109).

Despite the discrepancies seen among various studies, the ability to measure EE in mechanically ventilated patients may, at present, be one of the only assessment techniques available to investigate the efficacy of nutritional support. By accurately determining daily EE of individual patients, one can determine whether the amount of energy infused, the type and proportion of substrates infused and the method of nutrient infusion (enteral versus parenteral) will influence morbidity, mortality and length of hospital stay of the patient. It is therefore the purpose of this thesis to accurately evaluate an apparatus designed to measure EE and to determine daily EE in mechanically ventilated critically ill patients. It is anticipated that this will provide the necessary background for future studies that will be designed to investigate the efficacy of nutritional support of critically ill patients.

II Historical Perspective on Energy Expenditure

(i) Animal Respiration Experiments

Joseph Priestley in the seventeenth century was the first to recognize the relationship between life and a burning flame (66). Priestley observed that in a closed space, a flame made air unfit for a flame, a mouse made air unfit for a mouse, a flame made air unfit for a mouse and that a mouse would die at approximately the same time that the flame went out. From these observations he believed that both mouse and flame phlogisticate or give off a substance to the air in the same way. Although his explanation of combustion was later proven to be incorrect, Priestley's observations were paramount in the study of metabolism of living organisms.

In 1870, Lavoisier, a French chemist and mathematician, disproved the phlogiston theory proposed by Priestly. One would expect weight loss if a substance was released during combustion. Lavoisier found the opposite, the weight of products of combustion increased (66). He identified that a burning substance, a flame or an animal, removed a substance with weight from the air. He recognized this substance as an elementary gas that occupied approximately one-fifth of normal air. Because this substance produced carbonic, sulfuric and phosphoric acids when combusted with carbon, sulfur and phosphorus respectively, Lavoisier named it "oxygene" or acid-former.

Lavoisier recognized that animal heat was derived from the oxidation of the body's substance and he compared this experimentally to the heat liberated by a burning flame (66). He burned a known amount of carbon in an ice-chamber and recorded the amount of ice that melted. From this he calculated the amount of heat produced per unit of carbon. Similarly, he and a co-worker, Laplace, placed a guinea pig in an ice chamber and again observed the amount of ice that melted and calculated the amount of heat and carbon dioxide given off by the animal (67). They concluded that the source of heat produced by an animal was the oxidation of body substances.

(ii) The First Human Respiration Experiments

Lavoisier and Laplace were the first investigators to perform heat and respiration experiments on man (74). Although the methods used in their respiration experiments are not known, the results obtained were strikingly similar to those obtained today. Results from their study were:

(1) the quantity of oxygen required per hour by a fasting resting man was 24.0 liters when the ambient temperature was 26°C;

(2) the quantity of oxygen required per hour by a fasting resting man

was 27.0 liters when the ambient temperature was decreased to 12°C;

(3) the ingestion of food was accompanied by a rise in oxygen consumption of 14.0 liters of oxygen per hour above resting levels; and,

(4) during exercise, the quantity of oxygen consumed per hour may increase to 91.0 liters per hour or greater.

Lavoisier and Laplace had identified three major factors that influence oxygen consumption: ambient temperature, food and physical activity. From his experiments, Lavoisier developed the theory of combustion and metabolism which stated that both flame and animal consume oxygen combining it with organic substances to give off carbon dioxide and water and that, in animals, the major portion of heat is liberated when oxygen combines with organic substances in the animal's body. Although the first law of thermodynamics, the law of conservation of energy, was not proposed by Hess until 1840, Lavoisier had already linked together the theory of combustion and the metabolism of man.

(iii) The Importance of Protein In Energy Metabolism

Not until the mid-eighteen hundreds was it recognized that foods were made up of protein, carbohydrates, and fat and it was these organic substances that "burned" in the body and not pure carbon and hydrogen (74). In 1842 a German scientist, Liebig, suggested that the nitrogen excreted in the urine may be a measure of protein destruction in the body of man (74). Voit demonstrated the first nitrogen equilibrium in 1857, that is, the amount of ingested nitrogen was equal to the amount of nitrogen excreted in the urine (74). Voit studied a dog for fifty-eight days and found that the difference between the amount of nitrogen taken in and that which was excreted was less than one percent. This method of calculating protein metabolism was essential to the future confirmation of the relationship between human metabolism and the law of conservation of energy.

(iv) The Relationship Between Human Metabolism and the Law of Conservation of Energy

In 1894 a German scientist, Rubner, successfully constructed an animal calorimeter which could accurately measure both the amount of heat a dog produced (direct calorimetry) and the respiratory exchange (indirect calorimetry) (38). From respiration, the metabolism could be calculated and the heat production estimated. Rubner showed that the amount of heat liberated by the dog and the amount of heat calculated from the metabolism of the dog during a twenty four period spent in the calorimeter were the same. The amount of heat produced by a dog was equal to the heat of combustion of fat and protein catabolized minus the heat of combustion of the urine excreted. He therefore concluded that the metabolism was the source of heat loss from the body.

III Metabolism of Carbohydrate, Protein and Fat

Through the work of early investigators such as Lavoisier, Voit, Liebig and Rubner it has firmly been established that the amount of heat, carbon dioxide and water liberated and oxygen consumed by the metabolism of man or the combustion of foodstuffs is the same. It is appropriate to briefly review the combustion of foodstuffs *in vitro*. Consideration of heat produced as chemical energy from the oxidation of carbohydrate, fat and protein is basic to the understanding and measurement of energy metabolism in the human body.

(i) The Bomb Calorimeter

Principles used to measure heat production by direct calorimetry are best illustrated by a simple device known as a bomb calorimeter constructed by Riche in 1913 (40). The bomb calorimeter was used to measure the amount of heat liberated from combustion of various foodstuffs. A weighed amount of foodstuff was placed in the bomb, filled with oxygen at a high pressure (approximately 25 atmospheres) and then immersed in a known amount of water. Due to the high oxygen pressure, when the foodstuff was ignited instantaneous combustion resulted and caused a rapid increase in temperature of the bomb and the surrounding water. The calories of combustion were calculated, one calorie was equal to the amount of heat required to raise the temperature of one gram of water by one degree Celcius. The calorific value of various types of foodstuffs could be easily determined by this technique.

(ii) Respiratory Quotient

The respiratory quotient (RQ) is used to describe the relationship between volume of oxygen consumed and carbon dioxide produced during the chemical reaction of foodstuffs. The RQ is the volume of carbon dioxide produced divided by the volume of oxygen consumed.

(iii) Carbohydrate Metabolism

Carbohydrate is a major fuel source important to human metabolism. Starch, a complex polysaccharide made up of many small glucose molecules, can be expressed simply by the chemical formula $(C_6H_{10}0_5)n$. Once starch is digested and absorbed by the body it is carried by the blood as individual glucose molecules to body cells where it is oxidized to carbon dioxide and water. Heat is liberated during this chemical reaction. This reaction can be expressed as follows:

$$C_6H_{10}0_5 + 60_2 \rightarrow 6C0_2 + 5H_20 + \text{heat}$$

By calculating the molecular weights of the individual elements the following values are obtained (38):

	starch	oxygen	carbon dioxide	water
carbon	6 x 12 = 72		6 x 12 = 72	
hydrogen	10 x 1 = 10			10 x 1 = 10
oxygen	5 x 16 = 80	12 x 16 = 192	12 x 16 = 192	6 x 16 = 80
	162	192	264	90

The combustion of one gram of starch yields 4.2 calories and therefore combustion of 162 grams will produce 680.4 calories. The volume of oxygen consumed and carbon dioxide produced in this reaction is exactly equal at 134.34 liters. Since 680.4 calories are produced by the consumption of 134.34 liters of oxygen, for each liter of oxygen consumed during the combustion of starch, 5.065 calories are liberated. Therefore, the calorific value of starch is 5.065 calories per liter of oxygen consumption. The calorific value obtained from various carbohydrates is dependent on their particular chemical structure. Rubner determined that for the human diet, the average caloric value of one gram of carbohydrate was 4.1 (38). During carbohydrate oxidation, 6 molecules of carbohydrate are produced and 6 molecules of oxygen are consumed. Therefore, the RQ is always equal to 1.0.

(iv) Fat Metabolism

Triacylglycerols constitute more than 90% of dietary fat, with the remainder being made up of phospholipids, cholesterol, cholesterol esters, and free fatty acids (56). After ingestion, triacylglycerols are digested by various lipases of gastric, pancreatic and intestinal origin, emulsified and solubilized before transport from the intestine to the blood stream. From the blood they can be metabolized by numerous cells or transported for storage. The oxidation of fat can be represented by taking tripalmitin as an example (38):

$$\begin{array}{ccccccccc} C_{51}H_{98}O_6 & + & 72.5\ O_2 & \rightarrow & 51\ CO_2 & + & 49\ H_2O & & \\ 806 & & 2320 & & 2244 & & 822 & & \text{molecular weights} \end{array}$$

Each gram of animal fat produces approximately 9.5 calories and therefore 806 grams of tripalmitin would yield 7657 calories, requiring the oxidation of 1623 liters of oxygen. Each liter of oxygen consumed would therefore have a calorific value of 4.72. The average calorific value to be approximately the same for all fats (food or human) at 4.686 calories per liter of oxygen consumed (38). The RQ of tripalmitin is equal to 0.703 since 72.5 molecules of oxygen are required during the oxidation and 51 molecules of carbon dioxide are produced.

Studies in which animals have been fed large amounts of carbohydrate have demonstrated that carbohydrate can be metabolized to fat in the body (38). When geese were stuffed with cereal grain in order to produce pate rich in fat, it was noted that the RQ was as high as 1.33. This is because glucose requires only a small amount of oxygen for fat formation, but liberates a large amount of carbon dioxide. This can be demonstrated by the following stiochiometric reaction where palymitylstearyloleyglyceride ($C_{55}H_{105}O_6$) is formed from glucose (44):

$$13.5\ C_6H_{12}O_6 + 3\ O_2 \rightarrow C_{55}H_{104}O_6 + 26\ CO_2 + 19\ H_2O$$

The RQ in this reaction would be 8.67. In the human body, fat synthesis is indicated by an RQ value greater than 1.0. However the value seen is seldom greater than 1.3.

(v) Protein Metabolism

Unlike carbohydrates and fats which are generally considered as energy substrates for human metabolism, proteins are an integral part of structural and functional components of the body. Proteins constitute approximately 19% of the weight of the human body (57). Most proteins contain between 15 and 17.5% nitrogen. Muscle is roughly 70% water.

Proteins are digested by gastric pepsin to form large polypeptides which are further broken down to small peptides and free amino acids by pancreatic and intestinal proteases in the intestinal lumen. Small peptides and free amino acids are transported across the gut wall via specific transport mechanisms and into the bloodstream where they become available to body cells.

The catabolism and resynthesis of body proteins is a dynamic and continuous process with dietary proteins supplying the necessary amino acids. Dietary proteins intake in excess of "wear and tear" requirement results in deamination with the carbon skeletons being used to form glucose (gluconeogenesis) for energy production.

As first shown by Liebig, the amount of protein catabolism can be measured by nitrogen excretion in the urine (37). Since protein contains approximately 16% nitrogen, the loss of 1 gram of nitrogen in the urine represents the catabolism of approximately 6.25 grams of protein. In normal humans, the amount of nitrogen ingested is close to the amount excreted. In this situation an individual is said to be in nitrogen balance or equilibrium. Most normal diets contain 12 to 19 grams of nitrogen, although it has been shown that nitrogen equilibrium can be maintained at intakes of 5 to 7 grams per day (38). In disease, trauma, surgery and other critical illnesses, it is well known that protein catabolism greatly increases as reflected by large urine nitrogen losses (27,50,61).

The oxidation of protein within the body is incomplete. This was first demonstrated by Rubner who showed that the heat value of carbohydrate and fat metabolism in the body and by calorimetry was the same. However this was not true for proteins (74). The heat value of protein was higher when pure protein was burned in a bomb calorimeter than when metabolized in the human body (74). Protein metabolism in the human body results in heat loss in three different ways; respiration, feces and urine. The latent heat lost in urine and feces must therefore be deducted from the heat value of protein determined by calorimetry. Rubner showed that for every gram of nitrogen lost in the urine and feces, 9.35 grams of carbon dioxide was produced, 8.45 grams of oxygen was consumed and 25.98 calories were eliminated as heat (38). Rubner determined the average available energy from protein metabolism to be 4.1 calories per gram (38).

(vi) Non-Protein Respiratory Quotient

In performing respiratory experiments, if nitrogen excretion is measured, the amount of carbon dioxide production and oxygen consumption ascribed to protein metabolism can be deducted from the total expired carbon dioxide production and oxygen consumption. The remaining carbon dioxide production and oxygen consumption is attributed to fat and carbohydrate metabolism. After deductions, the remaining volume of carbon dioxide divided by the volume of oxygen is the non-protein RQ. Since the RQ of fat metabolism is approximately 0.701 and carbohydrate metabolism is 1.00, the proportions of fat and carbohydrates metabolized can be calculated from any non-protein RQ between these points. Lusk has constructed a table of RQ values from different proportions of fat and carbohydrate metabolized (73). Similarly DuBois constructed a triangular map of metabolism based on RQ values to describe the proportions of protein, carbohydrate and fat metabolized (36). It is important to remember that these types of tables show only net transformations within the body during a given period. It is conceivable that fat formation may occur at the same time as fat is broken down. However simultaneous formation and degradation may not be evident by the resulting RQ value.

The early studies on energy expenditure provided irrefutable evidence that the two following facts form the basis of indirect and direct calorimetry:

(1) At least over a few days, the amount of chemical energy ingested from foodstuffs is identical to the total amount of energy dissipated and excreted.

(2) The caloric value of fats, carbohydrates, and proteins and the amount of oxygen required for their combustion, determined by in vitro experiments, are the same values determined by in vivo experiments. That is, the amount of oxygen required to burn carbohydrate in a bomb calorimeter and the amount of heat, carbon dioxide and water liberated will be the same as that which is required for man or animal.

IV The Classical Studies on Energy Expenditure in Normal Men and Women

In 1892, the American scientist Atwater began the construction of a calorimeter capable of measuring heat production in man (74). With the help of Rosa, a physicist, the original Atwater-Rosa calorimeter was combined with respiration apparatus and was capable of simultaneously measuring heat production and carbon dioxide excretion. The original calorimeter was not capable of measuring oxygen intake. During the same time period as Atwater, Benedict constructed a similar apparatus capable of simultaneous measurement of respiration and heat production at the Nutrition Laboratory of the Carnegie Institute in Boston. These laboratories were followed by construction of many similar laboratories throughout the United States. The actual techniques used for these measurements will be discussed in detail later in this thesis under methods of determining EE.

(i) Energy Expenditure Based on Body Surface Area

The ability to measure basal metabolism in man and animals has produced great controversy as to how results should be expressed. Various researchers (19,48,49,80) during the early nineteen hundreds supported the concept that metabolism should be expressed with respect to body surface area, while others (12,15,31,55) believed that metabolic rate could not accurately be expressed in this way. The historical basis for measurement of metabolic rate as a function of body surface area originated with studies conducted by Rubner in the mid-eighteen hundreds and later became known as Rubner's law (75). Rubner's law stated that "the heat production in different animal species and man was proportional to the corresponding body surface area". The basic premise of Rubner's law was that if the body were viewed as a mass of cells with a constant heat production at the centre and if two spheres of unequal size were compared, loss of heat from the surface would be greater for the smaller sphere which would cool more rapidly due to the relatively greater exposed surface area. The heat eliminated would therefore be proportional to the surface exposed.

Based on Rubner's law, a German scientist, Meeh, in 1879 measured the surface area of six adults and ten children (33). Meeh used his measurements and the fundamental mathematical law that the surface of similiar solids are proportional to 2/3 of the power of their volume, to develop his surface area formula. Using body weight to represent volume, he determined that a constant of 12.312 when multiplied by the cube root of the weight in kg gave results which came within 7% of all the measurements he had made. Meeh's formula is expressed as follows:

$$S = k \sqrt[3]{W^2}$$

where: S = surface area in square meters,
k = constant of 12.312, and W = weight in kilograms.

The original Meeh's formula was not challenged until 1915 when Gephart and DuBois performed a number of experiments of basal metabolism of normal humans and humans with a variety of disease conditions (49). Gephart and DuBois found that actual measurements of body surface area on subjects deviated considerably from those calculated using Meeh's formula. In all instances Meeh's formula overestimated the measurements they had obtained. As a result, DuBois and DuBois performed numerous measurements of body surface area on men and women whose bodily forms varied markedly (33). The determination of body surface area was obtained from the sum of nineteen measurements of each body part times a constant. The results DuBois and DuBois obtained when compared to Meeh's formula showed that body surface area computed from Meeh's formula had an average inaccuracy of 16% and a maximum variation from normal of 36%. As a result of their findings, DuBois and DuBois developed a new "linear" formula or "height-weight" formula" (34):

$$A = W^{0.425} \times H^{0.725} \times 71.84$$

where: A = area in square meters, W = weight in kilograms
and H = height in centimeters.

This formula gave an average error of 1.5% and a maximum variation of ±5%. Since the establishment of DuBois and DuBois's "height-weight" formula, many subsequent researchers have used this derivation of body surface area as the standard means to describe and compare metabolic rates of both normal metabolism and metabolism during various disease conditions. In subsequent research based on body surface area, Aub and DuBois found metabolism decreased with increasing age (6). As a result of this research, Aub and DuBois published the Sage normal standards which are based on body surface area, age, and sex of the individual (41).

In opposition to body surface area being used as the standard to compare metabolic rate, Benedict suggested that careful analysis of metabolic measurements obtained from athletes (14), normal men and women (12,15) and normal and malnourished infants (13) did not support the conclusion that metabolism or heat output of the human body was proportional to body surface area. Benedict reported that numerous factors independent of body surface area such as age and athletic training will have a significant effect of basal metabolic rate (16). In a study comparing normal men and women, Benedict and Emmes found that the basal metabolism of normal men was 7% greater than women of the same height and weight and therefore the same corresponding surface area (15). Similarly, Benedict and Mommouth found that athletic individuals had a greater metabolism than non-athletic individuals of similar height and weight (14). Benedict suggested that the major reasons for these differences are two-fold. Firstly, the difference in body composition, the proportion of inert body fat and active protoplasmic tissue (commonly known today as lean body mass) has a major influence on basal metabolic rate. Secondly, the stimulus to cellular activity existing at the time the measurement is made will have a significant effect on basal metabolic rate. In conclusion, Benedict believed that there was no law that could be laid down to cover the important variables in the basal metabolism of an individual (16).

Prior to 1910, studies on basal metabolism of normal men and women were often performed in large respirometers in which small amounts of movement were allowed. Because it became well known that muscular activity can significantly alter metabolic rate, the results obtained in most studies prior to 1910 were not truly representative of the "basal" state and therefore could not be considered with subsequent comparisons (49). Basal metabolism has become universally accepted as referring to the heat production of an individual measured during the morning, 12 to 18 hours after the last meal with the individual completely at rest, lying comfortably in a thermally neutral environment.

(ii) Energy Expenditure of Normal Men and Women

In 1914, Benedict et al. were among the first to report the results of basal energy expenditure in normal men and women (11). The experiments were performed using the "universal respiration apparatus" designed at the Nutrition Laboratory at the Carnegie

Institute in Washington. Benedict et al. studied indirect calorimetry and/or direct calorimetry of 89 normal men and 68 normal women. All subjects were studied in the morning in a post-absorptive state (i.e. 12 hours following their last meal) during complete muscular repose lying on a calorimeter bed and had pulse rates less than 100 beats/min. Subjects remained completely still on the calorimetry bed for a one-half hour period prior to actual measurement. Interestingly, the authors report their results for heat production on the basis of body surface area using Meeh's formula. However, they plainly state that this was done for comparison purposes only and that they did not believe body surface area had any justifiable basis for expressing metabolic rate.

The results Benedict et al. obtained are presented in Table 1-1. The basal metabolic rates of normal men and women were 34.7 and 32.2 calories per square meter of body surface per hour, respectively.

Shortly after Benedict's publication on normal individuals, Gephart and DuBois (48) reported results on the basal metabolism of seven normal men between the ages of 20 and 50 years. The experiments were carried out on the Sage Bed Calorimeter at the Russell Sage Institute of Pathology. Gephart and DuBois reported the results they obtained using both indirect and direct calorimetry and found excellent agreement between the two methods (within 0.17%). The methods used to ensure a basal metabolic rate were very similar to those described for the Benedict experiment. The results of Gephart and DuBois are summarized in Table 1-2. Based on their own

TABLE 1-1

Energy Expenditure in Normal Men and Women (mean ± SD)*

Number and Sex of Subjects	Age (yrs)	Body Weight (kg)	Height (cm)	$\dot{V}CO_2$ (ml/min)	$\dot{V}O_2$ (ml/min)	Total EE (kcal/day)	Total EE/kg/body weight (kcal/kg/day)	Total EE/sq meter/day ($kcal/m^2/day$)	Total EE/sq meter/hr ($kcal/m^2/hr$)
89, M	26±8	65±11	172±8	196±27	235±29	1639±207	25.8±2.5	833±63	34.7±2.6
69, F	27±10	55±11	162±19	158±19	195±22	1354±150	25.4±3.0	772±64	32.2±2.7

* Adapted from: Harris JA, Benedict FG: A Biometric Study of Basal Metabolism in Man. Carnegie Institute of Washington, Publication No. 279, 1919.

TABLE 1-2

Average Results of Energy Expenditure in Normal Men (mean ± SD)*

Number and Sex of Subjects	Age (yrs)	Period Studied (hrs)	Body Weight (kg)	Body Surface Area-Meeh (M^2)	Calories Per Square Metre per Hour	Total Calories Measured In Each Experiment	
						Method of Indirect Calorimetry	Method of Direct Calorimetry
7, M	31±10	3±1	65±10	1.98±0.20	34.2±2.7	193.7±91.7	193.8±96.6

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* Adapted from: Gephart FG, DuBois EF: The determination of the basal metabolism of normal men and the effect of food. Arch Int Med 1915;15:183.

work and that of Benedict, the researchers concluded that 34.7 calories per square meter of body surface per hour was the average heat production of normal men between the ages of 20 and 50 years.

During the same year as Gephart and DuBois, Palmer et al. were conducting experiments on the basal metabolism of normal men and women at the Massachusetts General Hospital (88). They used the method of indirect calorimetry using the Benedict universal apparatus to study 8 men and 9 women. The averge results are presented in Table 1-3. Palmer's results were similiar to those reported by Benedict for men and women.

Following these three pioneering studies and with the development of a new surface area calculating technique, in 1916 Gephart and DuBois (49) reviewed their own results and those of Palmer et al. (88) and Benedict et al. (12) to compare basal EE using both the DuBois formula and the Meeh's formula for body surface area. Gephart and DuBois found that Meeh's formula overestimated body surface area and that the DuBois formula more accurately predicted actual surface area. Recalculated normal basal energy metabolism using DuBois's formula for surface area were 39.7 calories per square meter per hour for men and 36.9 calories per square meter per hour for women. These figures have become widely accepted as standards of metabolic rate for normal men and women.

(iii) The Harris and Benedict Equation

Two of the most widely used standard equations for the determination of EE for normal individuals and patients with various diseases are the linear regression equations developed by Harris and

TABLE 1-3

Observations of Normal Men and Women (mean ± SD)[*]

Number and Sex of Subjects	Age (yrs)	Body Weight (kg)	Body Surface Area-Meeh (m^2)	$\dot{V}CO_2$ (ml/min)	$\dot{V}O_2$ (ml/min)	Total EE/24 hr (kcal/day)	Total EE/kg/hr (kcal/kg/day)	Total EE/sq meter (kcal/m^2/day)	EE/sq meter/hr (kcal/m^2/hr)
8, M	28±3	72±11	2.11±0.21	197±25	238±21	1657±158	23.4±1.7	785±32	33.2±2.1
9, F	22±1	65±12	1.99±0.24	172±15	210±23	1461±146	23.1±2.9	739±61	29.9±2.0

[*] Adapted from: Palmer WW, Means JH, Gamble JL: Basal metabolism and creatinine elimination. J Biol Chem 1915;21:239.

Benedict in 1919 (55). These researchers studied the basal metabolism of 103 women and 136 men using the Benedict universal respiration apparatus at the Carnegie Institute. Because of their reluctance to accept the body surface area law as a basis for the establishment of normal standards for heat production, Harris and Benedict, from their results, developed a series of biometric correlation formulas. These formulas were based on stature, body weight, sex and age. The basal heat production for males and females predicted by Harris and Benedict were:

$$\text{male} \quad h = 66.4730 + 13.7516w + 5.0033s - 6.7550a$$

$$\text{female} \quad h = 655.0955 + 9.5634w + 1.8496s - 4.6756a$$

where: h = basal heat product for 24 hours, w = weight in kilograms, s = stature in centimeters, and a = age in years.

(iv) Harris and Benedict Equations Versus DuBois Standards for Prediction of Metabolic Rate

Subsequent to the publication of the Harris-Benedict equations, many researchers have studied whether DuBois's standard based on body surface area or Harris and Benedict's standards based on linear regression equations more accurately predicted basal metabolism of normal men and women. Boothby and Sandiford in 1922 showed that when the Harris and Benedict equations were mathematically transposed to predict body surface, the differences between the two methods were negligible (18). It was therefore doubtful as to which formula was more accurate. Nearly the same values for variation in height and weight were utilized in the prediction of heat production in subjects of average adult size (both by the heat formulas of Harris and Benedict and the formulas of DuBois and DuBois) regardless of the theoretic considerations of surface area underlying their derivation. However, a marked discrepancy between the two formulas was noted when age and sex were considered.

Boothby and Sandiford found marked differences in the value allotted to the age factor by DuBois and by Harris and Benedict. DuBois based his comparisons for age on calories per square meter of body surface and therefore obtained the same percentage decrease in energy expenditure for either small or large subjects of increasing age (6). On the other hand, the Harris and Benedict equation predicted that the same number of calories for a given increase in age was subtracted regardless of the individual's size (55). For example, DuBois standards predicted a 10% decrease in basal heat production for a man of 70 years of age of any size, as compared to a 20 year old man of similiar height and weight. On the contrary, for men of the same age but different sizes, The Harris and Benedict equation predicts that a large subject (124 kg, 200 cm) would have a smaller reduction (12.5%) in heat loss than a small subject (a 32% decrease for a 25 kg, 151 cm man). This is evident from the manner in which the Harris and Benedict equation has been expressed. Since it was unlikely that a small individual would show more than twice the percentage decrease in heat production for advancing age than a large man, Boothby and Sandiford concluded that the DuBois standard based on body surface area and age more accurately reflected the effect of age on basal energy metabolism.

Similarly, the effect of sex on basal metabolic rate was more accurately predicted using DuBois's standards than the equations of Harris and Benedict (18). DuBois used the same percentage difference in heat production for sex at any constant age regardless of the individual's size. In contrast, using the Harris and Benedict equation, one would obtain a markedly lower heat production for large women than for similar sized men but a greater heat production for a smaller woman than a similar sized man. This appeared to be in opposition to Benedict and Emmes results of 1915 where they showed that for all men and women of similar sizes, the metabolic rate of women was consistently about 7% lower for women than men (15). Boothby and Sandiford suggested that this assumption of reversed effect of sex on heat production for small subjects was not substantiated by any available data. They concluded that it was likely that both age and sex affected heat production of large and small subjects in the same direction and by the same degree.

Boothby and Sandiford concluded from their study that any large discrepancies seen between basal metabolism as predicted by the formulas of Harris and Benedict and DuBois and DuBois were unlikely the result of small differences in body surface area since both appeared to be in remarkable agreement. Instead, differences would more likely be attributable to the effect of age and/or sex. These investigators remarked that until Harris and Benedict could prove that the effect of age and sex were different for large and small individuals it appeared the DuBois formula for determinations of surface area and the DuBois normal standards of heat production for each square meter of body surface for age and sex was the best available method to predict normal heat production.

Boothby and Sandiford supported their conclusions by studying the basal metabolism of 8614 subjects (18). They studied basal metabolism of 172 normal men and women and 8487 men and women with a variety of disease conditions (such as chronic nervous exhaustion, cardiac neurosis, obesity, etc.). When comparing surface area by the DuBois standards and by the Harris and Benedict equation they found that in most instances there was agreement within 1%. Therefore only a slight difference in values was found when the metabolic rate was expressed with respect to surface area. However considerable variation existed in many instances between the two standards when age and sex were considered. Variations of 5 to 14% were commonly seen. Boothby and Sandiford found that for most persons, the basal metabolic rates were within ±10% of normal using the DuBois standards for age and sex with the exception of a few subjects who had definite diseases that were characterized by a pathological alteration in rate of heat production. However, when the Harris and Benedict equation was used, a smaller percentage of the same subjects fell within the 10% limits. The researchers therefore concluded that the DuBois normal standards for age and sex based on calories for each square meter of body surface area provided the best standards available for prediction of normal heat production.

In 1921 Means and Woodwell analyzed the methods used by DuBois, Harris and Benedict, and Dreyer by comparing these prediction methods using data from normal individuals (81). They found that the results were similar in predicting normal energy expenditure. Based on the fact that the DuBois formula had become the accepted standard in clinical practice and that the other two methods did not offer any improvement in accurately predicting basal metabolism. Means and Woodwell concluded that for uniformity purposes it was senseless to abandon old methods for new ones unless the new methods were shown to offer some advantage. Hence, it appears that by the end of the 1920's the DuBois standard was the preferred method of expressing basal metabolism of normal individuals.

V Early Studies of Energy Metabolism During Disease

(i) Energy Expenditure in Typhoid Fever Patients

The study of basal metabolism in various disease states evolved simultaneously with the studies of normal metabolism. One of the earliest reports on energy metabolism during disease was by Coleman and DuBois in 1915 (23). They reported an in-depth study on ten patients with typhoid fever. Heat production was measured indirectly and directly using the respiration chamber at the Russell Sage Institute of Pathology. Nine males between the ages of 12 and 60 (average age ± SD = 26±15) and one female of age 12 were studied. Basal EE was measured in the same way as previously described. Rectal temperatures were recorded on each day measurements were made. A summary of basal heat production measurements made on the first day of the study following admission are presented in Table 1-4.

Coleman and Dubois used 34.7 calories per square meter of body

Table 1-4

Summary Data for Patients with Typhoid Fever*

Sex and Age of Subjects	Number of Basal Measurements Performed	Rectal Temp at time of Study (°C)	Pulse Rate (beats/min)	kcal/sq meter/day (kcal/m^2/day)	% increase above normal basal of 34.7 (kcal/m^2/day)
M, 21	14	40.0	99	51.42	48
M, 24	6	39.1	78	45.26	30
M, 12	7	39.7	103	49.93	44
M, 24	5	39.9	112	54.01	56
M, 60	2	37.1	85	36.54	5
M, 14	2	39.0	90	45.44	31
M, 18	1	37.1	79	38.26	10
F, 12	1	37.1	78	43.13	24
M, 36	5	38.5	116	44.33	28
M, 35	1	39.2	63	48.18	39
mean ± SD	4±4	38.7±1.2	90±17	45.65±5.5	32±16

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* Adapted from: Coleman W, DuBois EF: Calometric observations on the metabolism of typhoid patients with and without food. Arch Int med 1915;15:188.

surface per hour as their standard for normal metabolism (based on Meeh's formula for calculating body surface area). These standards were not appropriate for 4 subjects who were less than 20 years of age, as it was well known at the time that standard metabolic rates of children are greater than those of adults. Nevertheless, they found that basal heat production at the height of fever to be approximately 40% above normal. Heat production rose and fell in a curve roughly parallel to body temperature. During their experiment, the total divergence between indirect and direct calorimetry methods was only 2.2%. From this they concluded that the law of conservation of energy applied to fever patients and that indirect calorimetry was an accurate method to assess basal heat production. Coleman and DuBois' observations of large elevations in metabolic EE with associated increased body temperature during typhoid fever were precedent to further study of metabolism during infection.

(ii) A Historical Report of Energy Expenditure in a Cancer Patient

Murphy et al. reported some of the first studies on EE in cancer patients in the early nineteen hundreds (85,86). They found increases of 44 and 52% above normal basal metabolism for patients suffering from myelogenous and lymphatic leukemia, respectively (85). In 1915, Murphy et al. reported a detailed case study on a 51 year old male suffering from chronic lymphatic leukemia (86). They studied sequential EE, nitrogen excretion and leukocyte levels in this patient prior to treatment and during treatment with Roentgen-ray and radium therapy. The patient's heat production was studied by direct and indirect calorimetry at the Russell Sage

Institute of Pathology. Results showed there was extremely close agreement between the measurements made by the two methods (0.4%). The pretreatment EE of the patient was 44% greater than normal. Following 5 days of Roentgen ray treatments, there was a slight decline in basal metabolism. However after 23 days during which 10 treatments were given, no further decline was noticed. The prolonged treatment had also failed to produce an aleukemic blood picture. Following radium therapy, however, a large decrease in both basal metabolism and leukocytic count occurred. Basal metabolism decreased to 47.7 calories per square meter of body surface or 36% above normal. The authors offered no speculation about the relationship between decreased leukocyte count and the change in metabolic rate.

During the early nineteen hundreds numerous reports such as those described appeared in the literature. One major use of basal metabolic rate measurements was for the clinical diagnosis and treatment of thyroid disease (82). This led to the widespread use of simplified respiration devices which in turn were abandoned with the development of improved techniques of evaluating thyroid function. The use of direct and indirect calorimetry diminished in the clinical setting and very few studies on energy metabolism during disease and illness were performed between 1930 and 1950. Many clinical conditions were treated on the basis of assumed knowledge of EE which had never been subjected to actual measurements.

VI Energy Expenditure Following Uncomplicated Injury and Trauma

In the past 25 years, there has been a resurgence of interest in the measurement and understanding of EE in acute conditions, especially those associated with major injury and sepsis. It has been recognized that these conditions are often associated with weight loss and loss of lean body tissue during hospitalization (45,63,105). Consequently the extent to which increased EE plays a role in these conditions is of great interest.

In 1932, Sir David Cuthbertson was among the first to study the physiological response to injury (27). He studied 7 male patients with injuries to their legs. The average age of the patients was 36±14 years (mean±SD). Basal oxygen consumption ($\dot{V}O_2$) was measured by analysis of the patient's expired air collected in a Douglas bag. Cuthbertson measured daily $\dot{V}O_2$ and nitrogen balance for up to 12 days post-injury. He found the initial 24 hour period post-injury was characterized by "depressed vitality" during which the patient had a subnormal temperature, anuria, and decreased heat production as reflected by reduced $\dot{V}O_2$. This phase is commonly known today as the "ebb" phase which is associated with hypovolemia and shock. Following this phase, he observed a period of increased body temperature, heat production and nitrogen excretion (flow phase). The $\dot{V}O_2$ appeared to increase in parallel with nitrogen excretion. Average maximum increase in $\dot{V}O_2$ above predicted normal values was 20 to 25%. Nitrogen output rose considerably during the fourth to eighth day and in some instances exceeded 23 grams per day. Cuthbertson concluded that a relationship existed between the extent of injury and "degree of reaction" (hypermetabolism) and that this reaction was extremely variable among individuals.

Cope et al. reported a study on metabolic rate and thyroid function in injured patients (25). They studied three different types of injuries. One group consisted of 12 severely burned patients with burns of 20 to 68% of total body surface area (TBSA). A second group was comprised of 3 moderately burned patients with burns of 15 to 20% TBSA. The third group of 13 patients, consisted of 1 normal, 6 elective surgical patients and 6 patients requiring emergency surgery for closure of perforated ulcers. Metabolic rate determinations were made indirectly from $\dot{V}O_2$. Cope found that patients suffering from large burns had a 30 to 60% increase in basal EE above normal. This elevation was observed for up to two months following the injury. Patients suffering from smaller burns (15 to 20% TBSA) had only slight increases in basal metabolism which returned to normal within a few days. For patients who underwent uncomplicated elective surgery, basal metabolism was slightly increased postoperatively but returned to the preoperative levels in 5 to 7 days. The six patients who underwent surgery for perforated ulcers showed an increase in basal metabolism of the same magnitude as severely burned patients. However, this increase lasted only one to three days postoperatively and rapidly returned to normal. For 8 severely burned patients and 1 moderately burned patient, uptake of iodine-131 by the thyroid gland as an index of thyroid function was normal. Cope observed that metabolic rate in severely burned patients remained greatly elevated during the initial post-injury weeks and did not decrease to normal until wound healing was virtually complete. He concluded that increased $\dot{V}O_2$ appeared to be proportional to the severity of the burn injury.

Kinney and colleagues have contributed several studies on the metabolism of injured patients (61,63,64,108,109). Early studies were performed using a Douglas bag technique by which the patient's expired gas was collected and analysed for short intervals several times during a twenty-four hour period (61). They found that in many instances postoperative measurements of EE did not increase above preoperative levels. Despite this finding, Kinney agreed with Cope's observation that a slight rise of approximately 5 to 15% in postoperative EE was usually observed. Protein oxidation was increased during the postoperative period as evidenced by increased nitrogen excretion. Further studies by Kinney's group using a more sophisticated system for measuring gas exchange in acutely injured patients showed that EE was 30 to 60% above normal for severe trauma with multiple fractures or gun shot wounds, 60% above normal for sepsis, and up to a 100% above normal for third degre burns (65).

VII Energy Expenditure in Patients with Infection and Sepsis

Fever, often seen during the postoperative period, following injury or in association with infection, is felt to result from a white cell mediated pyrogenic influence on the temperature regulating centre in the brain. In 1921, DuBois published a review on basal metabolism during fever suggesting that an increase in temperature was associated with a proportional increase in metabolic rate (35). DuBois based this theory on compiled data of basal metabolism measurements made during typhoid fever, malaria, tuberculosis, erysipelas, arthritis and following intravenous injection of protein. He found that out of a total of 137 experiments on this heterogeneous population, there was only a small variation in metabolic rate for a given temperature. DuBois concluded from his study that for every $1^{\circ}C$ rise in body temperature above normal, the basal metabolic rate increased by approximately 13%. Application of DuBois's rule during injury and injury complicated by infection has been disputed by further research. Cope et al. found that changes in daily $\dot{V}O_2$ post-injury were not always accompanied by changes in body temperatures (25). Other researchers have supported the fact that changes in body temperature following injury, surgery and/or infection are associated with variable responses in EE (52,53)

Changes in basal metabolism following injury is variable and often difficult to quantitate. General trends of EE for patients with uncomplicated surgery, multiple injuries, injury with pre-existing malnutrition and other abnormal conditions have been quantified by several authors and are often presented in the form of simple nomograms (65,111). Although such predictions may be valuable in estimating EE of various patient groups, their ability to accurately estimate EE of individual patients is limited, due to the large variability often seen within the groups. Elywn suggested that it is not uncommon for resting EE to be under or overestimated by 30% in hospitalized patients and that this error is further confounded when one tries to correct for stress, disease, food utilization and activity (45). This problem is further magnified for patients whose injuries are complicated by infection and sepsis. Superimposed infection can have an unpredictable influence on energy metabolism.

(i) Energy Expenditure in Spontaneously Breathing Septic Patients

Gump et al. studied $\dot{V}O_2$, whole body and splanchnic blood flow in patients with intraperitoneal infection (52). Fifteen patients (13 males, 2 females) considered to be acutely ill due to infection were studied. None were hypotensive or required mechanical ventilation or supplemental oxygen. Resting $\dot{V}O_2$ was within 15% of predicted normal values for 6 patients. In the remaining 9 patients, $\dot{V}O_2$ was increased by 19 to 44% above normal values. In opposition to DuBois's theory on fever, Gump et ~~al~~. found a poor correlation between body temperature and $\dot{V}O_2$. For the 6 patients with normal $\dot{V}O_2$, splanchnic blood flow was also normal. However for 9 patients with elevated $\dot{V}O_2$, splanchnic blood flow was increased. The authors concluded that splanchnic circulation may play a key role in hemodynamic and metabolic changes associated with fever and intraperitoneal infection.

Long studied the EE of six septic patients (70). Neither the criteria used to define sepsis or the type of infection present were reported. Energy expenditure was measured indirectly by analysing oxygen and carbon dioxide in patient's expired air using a flow system through a rigid head canopy. He reported a mean EE of 30.17± 5.56 calories per kilogram body weight per day which represented a 30% increase above the normal values.

(ii) Energy Expenditure in Mechanically Ventilated Septic Patients

Subsequent to these earlier reports of EE during sepsis in spontaneously breathing patients, accurate methods of indirect calorimetry for measuring gas exchange of patients requiring mechanical ventilation, became available. This further complicated the ability to predict EE during sepsis. That is, does the presence of sepsis in a patient capable of spontaneous respiration have the same effect on EE as in patients who require mechanical ventilation? Halmagyi and Kinney addressed this question by measuring metabolic rates of both septic and non-septic patients who required mechanical ventilation (54). Measurement of gas exchange was performed using a mass spectrometer to analyse both inspired and expired gases. In 10 non-septic patients, metabolic rate was found to be within predicted normal range with average $\dot{V}O_2$ of 126±20 ml per min per square meter of body surface. However the metabolic rate of septic patients was greatly elevated, $\dot{V}O_2$ was 184±33 ml per min per square meter of body surface or approximately 60% above normal predicted values. In a previous study, Halmagyi and Kinney found the mean $\dot{V}O_2$ of spontaneously breathing septic patients to be 38% greater than predicted normal values (53). From these observations, the authors concluded that hypermetabolism during sepsis appeared to be proportional to the clinical severity of the patient's condition.

An interesting study by Giovannini et al. further emphasizes the complexity of EE during sepsis (50). They performed gas exchange measurements on 99 mechanically ventilated critically ill surgical patients. Thirty-three patients studied were septic as defined by the presence of positive blood cultures and/or positive cultures from wound sites. Sixty-six patients were studied following surgical or nonsurgical trauma without septic complications. Their results showed that septic patients had significantly higher $\dot{V}O_2$'s and metabolic rates. Oxygen consumption was 173±50 versus 155±45 ml per minute per square meter of body surface and EE was 51±14 versus 45±13 calories per square meter of body surface per hour for septic and nonseptic patients, respectively. The level of metabolic rate corresponded to a mean increase above normal values (based on the Harris and Benedict equation) of 45% in septic patients and 34% in non-septic patients.

On further analysis of their data, based on clinical signs and patterns of peripheral oxygen extraction as reflected by mixed venous oxygen partial pressure ($P\bar{V}O_2$), Giovannini found significant differences within the septic group. For septic patients with high $P\bar{V}O_2$'s (equal to or greater than 42 mmHg), a pattern was observed which was characterized by more severe deterioration of clinical status including profound hypoalbuminemia, severe mental confusion, hypotension and increasing blood urea nitrogen. In contrast, patients with normal or low $P\bar{V}O_2$ (less than 42 mmHg) showed a more compensated response without signs of major metabolic abnormalities. Patients with high $P\bar{V}O_2$'s had a significantly lower $\dot{V}O_2$ and metabolic rate and a significantly higher cardiac index than patients with normal $P\bar{V}O_2$. Oxygen consumption was 135±58 versus 180±45 ml per minute per square meter of body surface, EE was 41±15 versus 52±13 calories per square meter of body surface per hour and cardiac index was 7.6±3.2 versus 4.6±2.3 liters per minute per square meter of body surface, for patients with low $P\bar{V}O_2$'s and high $P\bar{V}O_2$'s respectively. The authors concluded that septic patients in a more deteriorated stage of sepsis, despite increased needs, were unable to extract oxygen resulting in a decreased $\dot{V}O_2$ and metabolic rate. This study illustrated the variable and unpredictable response in $\dot{V}O_2$ and EE that can be seen during sepsis.

From the literature thus far reviewed, it is evident that accurate prediction of EE based on data from normal individuals for individuals with varying degrees of illness is probably an unrealistic endeavour. Unfortunately with such discrepancies seen in relatively simple populations, one is skeptical about the likelihood of being able to accurately and consistently predict energy requirements in the very complex critically ill patient population.

VIII Metabolic Studies of Critically Ill Patients

In the last 5 years with the development of portable metabolic carts that are capable of measuring gas exchange in spontaneously and mechanically ventilated patients, many studies have been and continue to be published on the EE of critically ill patients. The degree to which critically ill patients are hypermetabolic has become a major area of controversy among investigators.

Much of the discrepancy seen between studies on EE of the critically ill patient is likely related to the definition of "critical illness". In many of the following research papers, investigators have lumped together patients with numerous conditions such as inflammatory bowel disease, postoperative sepsis, multisystem organ failure, respiratory failure and so forth, to cumulatively represent critically ill patients. Whether or not one can justify collectively reporting EE should depend on the reproducibility of the results.

(i) Metabolic Studies in Spontaneously Breathing Patients

The earliest studies on patients considered to be critically ill were limited to spontaneously breathing patients since accurate techniques to measure EE of mechanically ventilated patients were not available. Rutten et al. in 1975 retrospectively investigated the energy requirements of 13 patients (98). From nitrogen balance studies they calculated the number of calories needed to be infused in order to attain positive nitrogen balance. Using predicted EE based on the Harris and Benedict equation, they determined that a multiplication factor of 1.75 was appropriate. Predicted EE using the Harris and Benedict, multiplied by 1.75, commonly became known as the Rutten formula.

Gazzaniga et al. performed measured EE experiments on a group of "acutely catabolic" patients to evaluate accuracy of the Rutten formula (47). They studied 50 spontaneously breathing patients using the Douglas bag technique. Seventeen of the patients received total parenteral nutrition at the time of the study with an average infusion rate of 45±3 calories per kilogram body weight per day. For these 17 patients, the type of illness, measured EE, predicted EE based on the Rutten equation (Harris Benedict equation x 1.75) and predicted EE based on the Harris and Benedict equation is included in Table 1-5.

Mean measured EE was 2825 and 2000 calories per day for males and females, respectively. Mean predicted EE based on the Rutten formula

Table 1-5

Energy Expenditure in Spontaneously Breathing Critically Ill Patients*

Sex	Age	Diagnosis	kcal/day			
			measured EE	Rutten-predicted EE	predicted EE from Harris and Benedict	% measured EE above predicted EE from Harris and Benedict
M	28	small bowel perforation, perforated pyloric ulcer	2900	2250	1286	126
M	42	extrahepatic biliary obstruction, splenectomy, liver laceration	3000	2250	1286	133
M	24	perforated stomach	3200	2850	1629	96
M	15	colectomy, peritonitis, hepatic and subphrenic abscess	2400	2900	1657	45
M	28	UGI bleeding, erosive gastritis	2750	2550	1457	89
M	39	carcinoma small bowel, nephrectomy	2350	2900	1657	42
M	20	Billroth I, splenectomy, thoracotomy pancreatectomy	2500	3150	1800	39
M	60	sigmoid perforation, subphrenic abscess	3100	2850	1629	90
F	55	common bile duct stricture	1300	2000	1143	14
F	45	ruptured cecum, subphrenic abscess	2400	2400	1371	75
F	34	sigmoid perforation, acute renal failure	2950	2250	1286	129
F	33	ileojejunal bypass takedown	1800	2400	1371	31
F	18	portal vein thrombosis	2150	2350	1343	60
F	65	small bowel obstruction, abscess	2050	1775	1014	102
F	55	small bowel obstruction	1500	1800	1029	45
F	65	carcinoma head pancreas	1625	2000	1143	42
F	65	small bowel obstruction	1700	1825	1200	63

* Adapted from: Gazzaniga AB, Polachek JP, Wilson AF, Day AT: Indirect calorimetry as a guide to caloric replacement during total parenteral nutrition. Am J Surg 1978;136:128.

was 2700 and 2088 calories per day for males and females, respectively. The investigators therefore concluded that the Rutten formula tended to underestimate caloric needs. Interestingly, for this sub-group of 17 patients, the range and variability in EE was enormous. Using the Harris and Benedict equation to predict normal EE, measured EE ranged from 14 to 129% above normal (63±43%, mean±SD) for females and 42 to 133% above normal (83±35%, mean±SD) for males. Nine of 17 patients had measured EE less than 75% above predicted values (45±16%). In view of the large discrepancies seen, one might question the validity of the investigator's conclusion that the Rutten formula underestimates energy requirements.

In response to the suggestion that EE is greatly elevated in the "acutely ill patient", Quebbeman et al. (89) and later Mann et al. (78) performed further studies. Quebbeman et al. studied a variable group of 67 spontaneously breathing patients including malnourished, post-surgical and severely catabolic patients. They found the average measured EE was 1,574±260 (mean±SD) calories per day for 39 males and 1,271±211 (mean±SD) calories per day for 28 females. Comparing their results with two predictive formulas, the Harris and Benedict equation (55) and the Aub and DuBois linear formula for body surface area (6), they found that neither formula accurately predicted measured EE. The investigators therefore developed two new linear regression equations, one based on body weight and one based on body surface area to more accurately predict EE. They concluded that the equations could accurately predict EE regardless of the patient's clinical diagnosis. These equations have not been validated by subsequent studies.

Mann et al. in a more recent study evaluated accuracy of the Rutten formula for predicting EE of 50 "acutely ill" patients (78). Energy expenditure was measured by indirect calorimetry using a portable metabolic cart in both mechanically ventilated and spontaneously breathing patients. All patients received total parenteral nutrition at the time of study. Table 1-6 includes the results from their study.

Mann et al. found that predicted EE based on the Rutten formula greatly overestimated caloric needs by approximately 49%. They reported that an average caloric replacement of 16% above predicted EE based on the Harris and Benedict equation was appropriate. Validity of this conclusion based on this data is questionable. Firstly, the factor of 16% was derived from mean values of the diagnostic groups, and variability between patients within the different groups was not reported. Therefore the number of patients with EE's possibly deviating from this value is not known. Secondly, the range of percentage increase in measured EE above predicted EE for different diagnostic groups of patients was 7.9 to 37.4%. For 11 patients, mean percentage increase was greater than 35%. Therefore using a mean factor of 16% above predicted normal requirements to quide nutritional intake would lead to substantial underfeeding in a large number of patients.

(ii) Metabolic Studies in Mechanically Ventilated Patients

With the development of gas exchange techniques capable of accurately measuring the EE of mechanically ventilated critically ill

Table 1-6

Energy Expenditure in Acutely Ill Surgical Patients (mean ± SD)*

Diagnostic Group	Number of Patients	Mean Age	Caloric Intake (kcal/day)	Measured EE (kcal/day)	Rutten-predicted EE (kcal/day)	Predicted EE (kcal/day)	% Measured EE above predicted EE
inflammatory bowel	6	64	2620	1840	2984	1705	8
peptic ulcer disease	4	75	2762	1561	2492	2492	10
pancreatitis	5	52	2369	1664	2554	1459	14
infarcted or ischemic bowel	5	64	2192	2079	2663	1522	35
bowel obstruction and fistulas	7	62	2729	1749	2628	1502	16
cancer	14	62	2250	1535	2450	1400	10
vascular complications	6	64	2436	1971	2509	1434	37
other complications	4	64	2352	1730	2769	1582	9

* Adapted from: Mann S, Westenskow DR, Houtchens BA: Measured and predicted energy expenditure in the acutely ill. Crit Care Med 1985;13:173.

patients, the effect of mechanical ventilation on EE was brought forth. Burzstein et al. addressed this question by studying 20 postoperative patients, 8 patients with multiple injuries, 6 with severe burns, 3 with postoperative septic complications and 3 with coma (21). Each patient served as his/her own control and measurements were made before and after mechanical ventilatory support. Mean $\dot{V}O_2$ during spontaneous respiration was 397±146 ml per minute and during respiratory support on mechanical ventilation was 303±117 ml per minute. This represented a significant reduction in $\dot{V}O_2$ of 24%. Burzstein concluded that in critically ill patients the oxygen cost of spontaneous respiration can be increased up to 30% above normal value.

Savino et al. also investigated the contribution of work of breathing to EE in 20 critically ill surgical patients (99). They studied 14 multiple trauma patients, 3 postoperative surgery patients, and 3 postcoronary artery bypass patients. Indirect calorimetry was performed using a portable metabolic cart, the MGM/TWO Gas Monitor. Gas exchange was monitored continuously over a 1 hour period during both assisted mandatory ventilation (AMV) and intermittent mechanical ventilation (IMV). Both $\dot{V}O_2$ and EE were significantly higher, 11.8 and 10.7% respectively, while patients were on IMV compared to AMV. While on AMV $\dot{V}O_2$ was 307±51 ml per minute (mean±SD) and EE was 2,128±341 calories per day. On IMV the $\dot{V}O_2$ was 348±55 ml per minute and EE was 2,380±369 calories per day. Mean percentage increase in measured EE above predicted EE was 28±19% during AMV (range 2 to 70%) and 43±21% during IMV (range

20 to 94%). The investigators concluded that patients supported on assist mode ventilation had decreased work of breathing as reflected by lower $\dot{V}O_2$ and EE and that the Harris and Benedict equation inaccurately predicted EE.

In opposition to large increases in EE reported in earlier studies, several recent studies (7,108,109) have proposed that critically ill patients are not highly hypermetabolic and do not have large increases in EE. Baker et al. investigated EE of a group of 20 critically ill patients admitted to the Respiratory ICU at the Toronto General Hospital (7). All patients required mechanical ventilatory support. Patient descriptions, predicted EE using the Harris and Benedict equation, measured EE, and percentage increase in measured EE above predicted EE are presented in Table 1-7.

The authors suggest that their data support the contention that the critically ill are only modestly hypermetabolic and exhibit only small increases in EE above normal. They found that mean percentage increase in measured EE above predicted EE to be only 4.6%. They concluded that critically ill patients require a modest excess in calories, approximately 15 to 30%, to meet caloric requirements. On review of the data presented in Table 1-7, such a conclusion could be questioned. Discrepancies between measured and predicted EE for individual patients are extremely variable. Measured EE ranged from -46.2 to 123.3% of predicted values and the mean percentage increase calculated from the raw data was 4.5±37.6%. Although the mean percentage increase in measured EE was only 4.6%, it is unlikely that this mean value is of importance when the variability within the data

Table 1-7
Energy Expenditure in Mechanically Ventilated Critically Ill Patients*

Sex	Age	Diagnosis	Predicted EE (kcal/day)	Measured EE (kcal/day)	% Measured EE above predicted EE (kcal/day)
F	37	Ruptured sigmoid diverticulum, peritonitis, ARDS	1492	1952	30.8
M	27	Ruptured aortic aneurysm, aspiration pneumonia	1609	1935	20.3
M	46	Gastric perforation, peritonitis	1949	1955	1.0
F	20	MVA, multiple injuries, intracerebral bleed	1494	804	-46.0
F	49	CA pancreas, whipple procedure, ARDS	1299	1504	15.8
M	48	Trauma, multiple fractures, ARDS	1824	1921	5.3
M	62	Guillain-Barre, cardiac arrest	1618	1548	-4.3
M	37	Pancreatitis, peritonitis, ARDS	ND	ND	ND
M	39	Esophageal perforation, mediastinal abscess	1513	1725	14.0
F	29	Viral encephalitis, staphylococcal pneumonia	1580	1030	-34.8
M	54	Necrotizing pneumonia, pancreatitis	1451	1545	6.5
F	72	Colon resection, fecal fistula, pulmonary embolus	1324	1516	14.5
M	21	MVA, multiple injuries	2008	1793	-10.7
F	44	MVA, multiple injuries	1072	2394	123.3
M	57	Multiple injuries, fat embolism, sepsis	ND	ND	ND
M	60	Necrotizing pneumonia	1616	1025	-36.6
M	20	Cystic fibrosis, pneumothorax, necrotizing pneumonia	1328	1241	-6.6
M	42	Intestinal perforation, peritonitis	1881	1569	-16.6
M	39	Pancreatitis, peritonitis	1759	2360	34.2
M	72	3° burn, sepsis	1621	1155	-28.7

ARDS - adult respiratory distress syndrome; MVA - motor vehicle accident; ND - not determined

* Adapted from: Baker JP, Detsky AS, Stewart S, Whitwell J, Marliss EB, Jeejeebhoy KN: Randomized trial of total parenteral nutrition in critically ill patients: metabolic effects of varying glucose-lipid rations as an energy source. Gastroenterology 1984;87:53-59.

is so large. From this data, their conclusion that there is only a small degree of hypermetabolism seen in critically ill patients, cannot be supported.

Weissman et al. have reported numerous studies on EE in critically ill patients in the past few years (107,108,109). A recent report compared measured EE to predicted EE by two commonly used predictive formulae, the Harris and Benedict equation and the Aub and DuBois standards based on body surface area (109). A carefully defined subgroup of the critically ill patient population was studied. Forty mechanically ventilated postoperative patients who were hemodynamically stable, noncomatose and nonseptic were studied. Indirect calorimetry was performed using a portable metabolic cart. They found that measured EE correlated poorly with predicted EE. For the Harris and Benedict equation the correlation coefficient was 0.57 and for the Aub and DuBois standards the correlation coefficient was 0.59. Mean resting EE was 20.9±4.8 calories per kilogram per day or 819.5±158.3 ml per square meter of body surface per day. The authors pointed out the large variability seen in the data suggesting that it was likely due to many factors present in the critical care setting, including the amount of sedation administered, nutritional intake and the clinical condition of the patient. However, despite large variability in the data, they concluded that patients were not profoundly hypermetabolic since measured resting EE averaged only 3.8% above predicted EE. They also concluded that estimation of EE on the basis of predictive formulas to which arbitrary activity and injury factors are added may result in significant overfeeding. These researchers emphasized that the role of standard predictive formulas for reliable estimation of EE in critically ill patients should be seriously questioned. Although this report describes a small increase in measured EE above predicted EE, it should be remembered that the patient population studied represents only a small subgroup of the critically ill patient population. Whether or not a similiar degree of a hypermetabolism is applicable to other groups of critically ill patients, such as postoperative trauma patients complicated by sepsis, acute renal failure, acute pancreatitis, multisystem organ failure, etc. has not been determined.

A study performed by Bartlett and colleagues in 1982 on EE associated with multiple organ failure accurately addresses the issue of EE during critical illness (9). The authors did not attempt to fix a definitive value to the percentage increase of measured EE above predicted EE. Instead, they suggested that the large variability in the results supports the need to directly measure EE for management of the nutritional requirements in critical illness. Estimation of caloric requirements was found to be only generally related to measured EE and therefore estimations of EE resulted in wide swings of hypercaloric and hypocaloric feedings. Since both extremes are potentially related to significant complications, the need for direct measurement of EE in this group of patients is well supported.

IX Early Methods Used To Determine Energy Expenditure in Man

(i) The Atwater-Rosa-Benedict Calorimeter

At the turn of the 20th centry, a large number of respiration chambers for human experiments were being constructed in Europe and North America. A respiration chamber, by definition, refers to an apparatus capable of simultaneously determining EE by measuring heat loss (direct calorimetry) and gaseous exchange (indirect calorimetry) (40). Probably the best known apparatus of this type was constructed by Atwater, Rosa and Benedict in Middleton, New York. The Atwater-Rosa-Benedict Respiration Calorimeter was the prototype design from which most other respiration chambers were patterned. The apparatus was divided into two fundamental parts, one for measuring gaseous exchange and the other for measuring heat production of a subject. Lusk published a detailed description of the Respiration chamber built at the Russell Sage Institute of Pathology which was based on the principles of the Atwater-Rosa-Benedict Respiration Calorimeter (71).

The chamber was large enough for a subject to lie or sit comfortably in the apparatus. The air within the chamber was purified by drawing it out of an opening through a system of absorbers and then returning it to the box. The air first passed through hydrogen sulfide to remove the water, then through a bottle containing hydrogen sulfide to absorb the moisture taken from the soda lime. The gain in weight of the first bottle containing hydrogen sulfide represented the water produced and the gain in weight of the second and third bottle represented the amount of carbon dioxide absorbed. Both carbon dioxide and water produced by the subject was removed by this method. Oxygen was simultaneously added to the chamber from an oxygen cylinder in order to replace the oxygen the subject consumed from the air. The amount of oxygen consumed was determined from weighing the cylinder prior to and at the end of the experiment. The methods of measuring gas exchange was validated by alcohol checks, where the actual oxygen consumed and RQ produced when ethyl alcohol was burned within the system could be compared to known values.

The measurement of heat production was the sum of two components. Approximately one-quarter of heat loss from the body was through water vapor. This was determined by weighing the amount of water removed by the hydrogen sulfide. At 20°C the latent heat in 1 gram of vaporized water is equal to 0.586 calories. By knowing the weight of the hydrogen sulfide bottle before and after the experiment, heat loss could be determined. The second component involved the measurement of heat loss by radiation and conduction. No heat loss could occur through the chamber walls. Heat produced by a subject was removed by a current of cold water flowing through copper tubes suspended from the upper wall of the chamber. By knowing the temperature of the ingoing and outgoing water and the quantity of water flowing through the pipes in a given time, the quantity of heat loss could be calculated.

Respiration chambers proved to be extremely accurate methods of simultaneously measuring heat production and gaseous exchange to determine EE (23,48,49). The major disadvantages were their large size, the relatively long period of time (2-12 hrs) needed for study, and operational costs. Although some respiration chambers are still in use today, they are mainly used to study obesity for which long-term energy balance (often greater than 24 to 48 hrs) is of interest (29,58,104). Obviously such lengthy studies are not practical and often not possible for application to hospitalized patients and especially not adaptable for use on mechanically ventilated critically ill patients. As a result, in the clinical setting, large calorimeters have gradually been replaced by smaller apparatuses which measure gaseous exchange only.

(ii) The Zuntz and Geppart Apparatus

Various methods for measuring gaseous exchange have been developed. One of the earliest systems was developed by Zuntz and Geppart (40). A subject would lie motionless on a cot for a one-half hour period prior to testing. The nostrils were tightly clamped by a nose clip and expired air was collected through a mouth-piece which was connected to a large gas meter. A one-way valve allowed the patient to draw air in from the room. Patient's expired air was forced through the meter to measure expired volume and at the same time a sample of expired gas would enter into burettes in a water bath for gas analysis. Tests lasted approximately 10 to 15 minutes. Expired carbon dioxide was measured by caustic potash and oxygen was measured by yellow stick sulfur. Carbon dioxide production and oxygen consumption could be calculated by knowing the length of time of the experiment, volume of expired air, volume of carbon dioxide produced and volume of oxygen consumed. The Tissot apparatus employed the same techniques with the exception of measuring expired volume by a displacement Tissot spirometer instead of a gasometer.

(iii) The Benedict Universal Apparatus

In 1909, Benedict developed the Benedict Universal Respiration Apparatus which was a closed system of measuring gas exchange by isolating the patient's respiratory tract (40). The subject was attached to a system of pipes that were connected to the respiratory apparatus by means of a mouth-piece and nose clip. The same air was breathed over and over. Water was removed by hydrogen sulfide and carbon dioxide was removed by soda lime and oxygen, as it was consumed, was replaced into the system by an oxygen cylinder. The volume of inspired and expired air was measured by a spirometer. Carbon dioxide and oxygen consumption could be easily calculated.

(iv) The Douglas Bag Technique

In 1911, Douglas first described what is now well-known as the Douglas bag technique (30). All the patient's expired air was collected in a large vulcanized rubber bag (30 to 100 litre capacity). The major advantage of this device was that it was lightweight and portable and could be carried on the subject's back. A mouthpiece was supported by a head harness which was connected to the Douglas bag. On expiration, a large three-way valve directed all expired air into the bag. At the end of the experiment, the volume collected was measured by a meter and a sample of expired gas was removed for carbon dioxide and oxygen analysis.

Shepard published a critique of the Douglas bag technique and suggested that errors in measurement could be of two types (102).

Firstly, there may be a gross loss of gas contents due to faulty technique. Secondly, there may be selective loss of gases attributed to diffusion through pores of the rubber bag. The bag should be emptied shortly after completion of the experiment, within 10 to 15 minutes in order to minimize the diffusional error. Shepard found that when a 100 litre Douglas bag was filled with 25, 55 and 65 litres of 100 percent oxygen, the diffusion rate of oxygen from the bag was approximately 150, 270 and 200 ml per hour, respectively, and the diffusion of nitrogen into the bag from the outside was approximately 75, 100 and 80 ml per hour respectively. Such factors are likely insignificant when studies are performed at room air concentrations. However when studying ventilated patients who require high concentrations of oxygen, diffusion of oxygen out of and nitrogen into the bag will have a more pronounced effect on the results obtained. Meticulous care in gas collection using the Douglas bag or any other technique is required to prevent erroneous results.

With increasing technology, many types of gas exchange methods have evolved. Although the devices used to measure gaseous exchange may be varied, all systems must contain components that will accurately measure carbon dioxide and oxygen concentrations and expired gas volume. Many systems, home-made (1,61,62) and commercially manufactured (42,78,91,99,109) are presently being used in the clincial setting.

Kinney et al. began using the Douglas bag technique to measure EE of hospitalized patients (61). However, such a technique was limited to patients capable of cooperating with the test procedure. This often eliminated the ability to study acutely ill patients who commonly exhibited increased minute ventilation because of the additional work of breathing caused by tight fitting face masks or mouth-pieces (65).

(v) Kinney et al's Head Canopy System

As a result, Kinney's group developed a more suitable head canopy system which was non-invasive and eliminated the attachment to the face or airway (62). This system permitted long, continuous, comfortable measurement of gas exchange in more acutely ill spontaneously breathing patients. A clear plastic head canopy was securely fastened around the subject's neck to prevent any leaks. The canopy was ventilated with an air flow of approximately 40 litres per minute pumped from a source of filtered air-conditioned air. The outlet air was directed through a flow system and samples were pumped into a carbon dioxide and oxygen analyzer for gas analysis. The system could be adapted to deliver up to 40% oxygen to spontaneously breathing patients whose clinical condition required a high level of oxygen. Systems such as that designed by Kinney et al were a step closer to measuring gas exchange in ill spontaneously breathing patients. However, the head canopy system was incapable of measuring energy exchange in patients requiring mechanical ventilation.

X Portable Automated Carts For Measurement of Energy Expenditure

(i) Principles of Gas Exchange

Increasing interest led to the development of many portable systems specifically designed to measure the EE of hospitalized patients. Norton has reviewed the principles that apply to most of these systems (87). Oxygen consumption is calculated by the following formula:

$$\dot{V}O_2 = \underset{\text{inspired oxygen flow}}{[\dot{V}_I \times F_IO_2]} - \underset{\text{expired oxygen flow}}{[\dot{V}_E \times F_EO_2]}$$

where $\dot{V}_I$ and $\dot{V}_E$ are the inspired and expired ventilation, and F_IO_2 and F_EO_2 are the inspired and expired fractions of oxygen, respectively. The inspired air is separated from the expired air by a non-rebreathing valve. The expired air is collected, gas composition analyzed and its volume measured, thus providing the terms of $\dot{V}_E$ and F_EO_2. The F_IO_2 is not measured and is assumed to be normal room air containing 20.93% oxygen. The inspired volume ($\dot{V}_I$) is calculated from the Haldane transformation as follows:

$$\dot{V}_I = \dot{V}_E\,[F_EN_2 / F_IN_2]$$

where F_IN_2 and F_EN_2 are the inspired and expired nitrogen concentrations of the air. The F_EN_2 is usually calculated from Dalton's law of partial pressures where:

$$F_EN_2 = 1 - [F_EO_2 + F_ECO_2]$$

Therefore, by replacing the appropriate variables, $\dot{V}O_2$ can be expressed by the following equation:

$$\dot{V}O_2 = [F_IO_2 \frac{F_EN_2}{F_IN_2} - F_EO_2] \ \dot{V}_E \text{ STPD}$$

where $\dot{V}_E$ STPD refers to the expired minute volume corrected to standard pressure and temperature.

(ii) Components Used to Measure Gas Exchange

Classical experiments of gas analysis using wet chemistry techniques have been replaced by more convenient techniques that are as accurate and have faster response times. Measurements of oxygen can be carried out by using various techniques such as polarographic cells, zirconium oxide cells and paramagnetic cells. Carbon dioxide analysis is commonly made using a non-dispersive infrared cell. Volume of expired gas can be measured in many ways. The most direct approach is to collect all the expired air in a large bag and measure the volume by evacuating the bag through a displacement gasometer, a dry gasometer or into a spirometer. This requires the collection and transport of large volumes of gases which is not practical in the hospital environment. Therefore, volume measurement of most present day portable systems is performed by measuring flow and integrating this to obtain volume. A turbine flow transducer that spins as gas flows through it, is used in some systems. Others utilize a pneumotachograph which measures flow-dependent differential pressure. One of the major disadvantages of these systems is the non-linearity of the transducers at low flow rates. The discussion of specific analyzers and flow devices used to measure gas concentration volumes will be limited to the system used in this thesis.

In addition to measuring expired volume and concentrations of carbon dioxide and oxygen, it is also necessary to measure the barometric pressure, temperature of expired gases and the length of time of the study. Actual volume measurements must be corrected to standard conditions ($0^{o}C$, 760 mm of mercury pressure and 0% water vapor). Most automated portable systems available today include fittings for connecting the patient to the system, oxygen and carbon dioxide analyzers, a volume measurement device, temperature transducer and a computer to handle, collect, process and compute results.

(iii) Principles of Gas Exchange Measurements in Mechanically Ventilated Patients

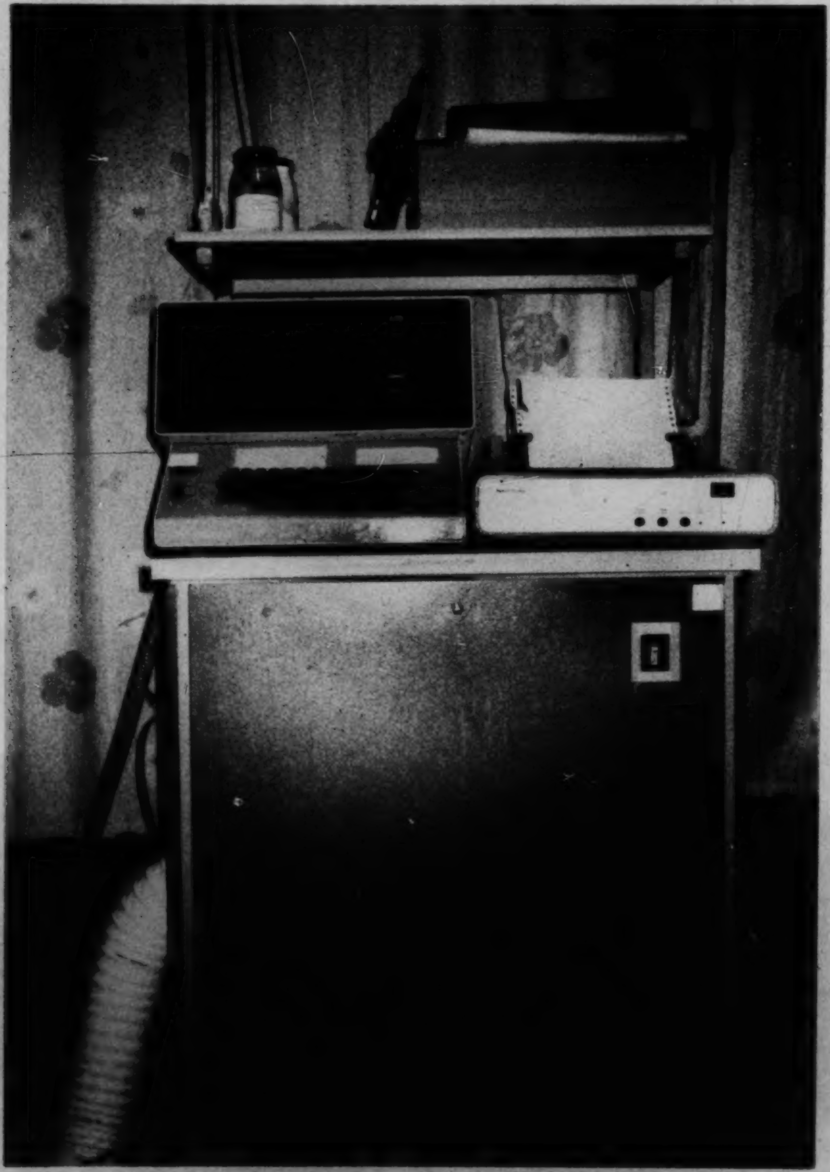
Only recently have automated portable systems, originally designed for exercise studies, been adapted to measure gaseous exchange in mechanically ventilated patients (41,78,99,109,110). The major modification required to the existing systems was the capability of continuously measuring the fraction of inspired oxygen (F_IO_2) received by the mechanically ventilated patient who often received an F_IO_2 above that of room air. Measurement of F_IO_2 is usually accomplished by connecting a sample line from the inspiratory limb of the patient's ventilatory circuit. By computer controlled time intervals, samples of inspired and expired oxygen concentrations are analyzed by the oxygen analyzer (usually at 30 second intervals). Computation of $\dot{V}O_2$ is based on the equations previously described, except that the actual measured F_IO_2 value replaces the previously assumed F_IO_2 value of 0.2093. Because both F_IO_2 and F_EO_2 cannot be simultaneously measured by a single oxygen analyzer, most systems assume that the F_IO_2 measured during a set time interval will correspond to the F_EO_2 value measured immediately preceding or following that interval. Such an assumption may not always hold true and therefore the ability to maintain the F_IO_2 within a narrow range is necessary to ensure accurate results. Browning recently addressed this problem and found that large fluctuations in F_IO_2 values could lead to considerable error in the results obtained (20). This error could be reduced by using an accurate external oxygen blender to provide the desired F_IO_2 level instead of relying on the internal blender of the ventilator.

(iv) The Gould 9000 IV Computerized Pulmonary Function Cart

The Gould 9000 IV Computerized Pulmonary Lab-Ventilator Option is the portable automated system used to measure gas exchange in this thesis (Figure 1-1). The 9000 IV was originally designed to perform pulmonary exercise testing and gas exchange measurements of spontaneously breathing subjects (51). It has been used extensively for the measurement of respiratory function during the training of Olympic athletes. Recently the system has been modified such that it can be used to measure gas exchange of both spontaneously breathing and mechanically ventilated patients. The system contains four major components: a 32K random access memory (RAM) computer with a cathode ray tube (CRT) real-time graphics display and memory printer/plotter; a dry-rolling seal spirometer; an infrared carbon dioxide analyzer; and a paramagnetic oxygen analyzer.

FIGURE 1-1

Photograph of the Gould 9000IV Computerized Pulmonary Function Cart used to measure energy expenditure in mechanically ventilated patients.



The dry rolling seal spirometer is used to measure minute ventilation and respiratory rate. Gas volume is measured by volume displacement of a horizontally mounted ten litre spirometer. The moveable piston with fixed cylinder is displayed by air volume. A flexible silicone dry rolling seal ensures that air-tight integrity is maintained. Volume measurement is made via direct mechanical linkage of the piston rod to an analog potentiometer. For each litre of piston displacement, the potentiometer registers a 1 DC volt change, establishing a direct relationship between volts produced and volume displaced. A thermometer probe is located within the spirometer and conversion of volume to BTPS units is computated automatically prior to print-out or display on the CRT screen.

The paramagnetic oxygen analyzer uses the physical characteristic of oxygen molecules being strongly attracted to a magnetic field (Figure 1-2).

The infrared carbon dioxide analyzer is based on the principles that each gas has its own unique light absorption pattern and that the amount of energy absorbed is a function of gas concentration (Figure 1-3). The specifications and accuracies of the oxygen analyzer, carbon dioxide analyzer, spirometer, and temperature probe are included in Table 1-8.

XI Limitations and Sources of Error in Measuring Gas Exchange in Mechanically Ventilated Patients

The measurement of oxygen and carbon dioxide concentrations and the volume of exhaled gas are necessary for the calculation for

FIGURE 1-2

The internal diagram of the paramagnetic oxygen analyzer. Varying concentrations of oxygen will alter the magnetic forces acting on a test body (two nitrogen filled quartz spheres joined together by a connecting tube in a dumbell configuration). The dumbell is suspended at the midpoint and surrounded by a series of electromagnets. The position of the dumbell is determined by the magnetic forces acting on it. A light beam is projected onto a mirror attached to the center of the dumbell and is reflected onto a pair of light sensitive detector cells (photocells). The magnetic field acting on the test body is altered when oxygen enters the analyzer which causes the dumbell to rotate. Rotation of the dumbell is detected by displacement of the reflected light source across the photocells. This causes the output of the photocells to change. The change is proportional to the concentration of oxygen surrounding the dumbell.

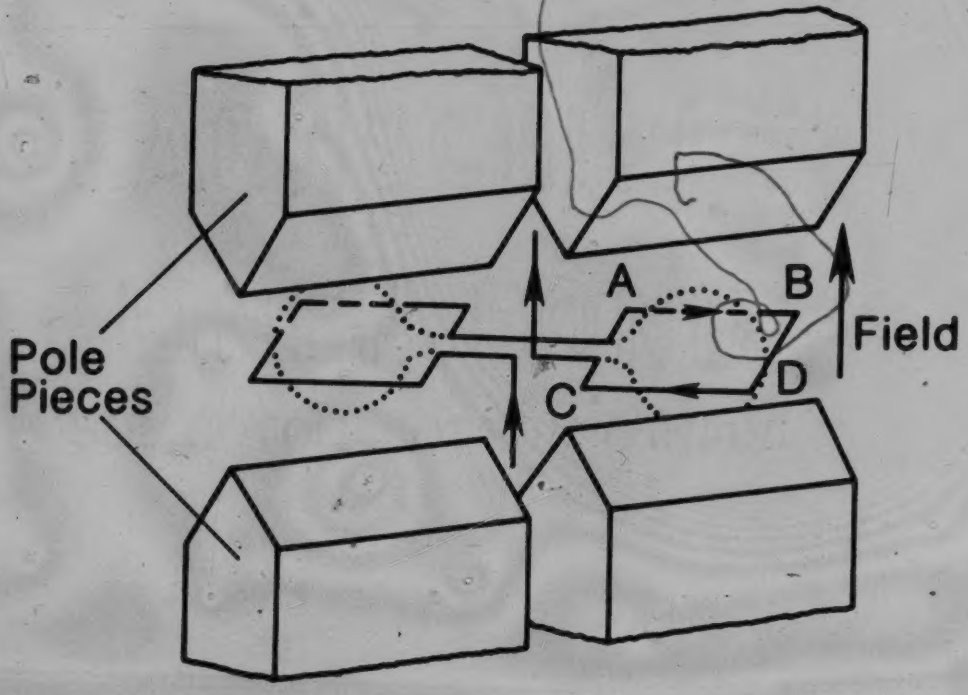


FIGURE 1-3

The internal arrangement of the sample cell used to measure carbon dioxide concentration in the infrared carbon dioxide analyzer. Infrared energy of a specific wavelength is passed from the source through an optical fibre and the sample cell. The amount of energy not absorbed by the gas in the sample cell will exit the sample cell and collect at the opposite end of the optical assembly. Accurate measurement of carbon dioxide concentration in the sample cell is achieved by comparing the output signal with zero gas in the sample cell to the output signal when the gas is present in the sample cell.

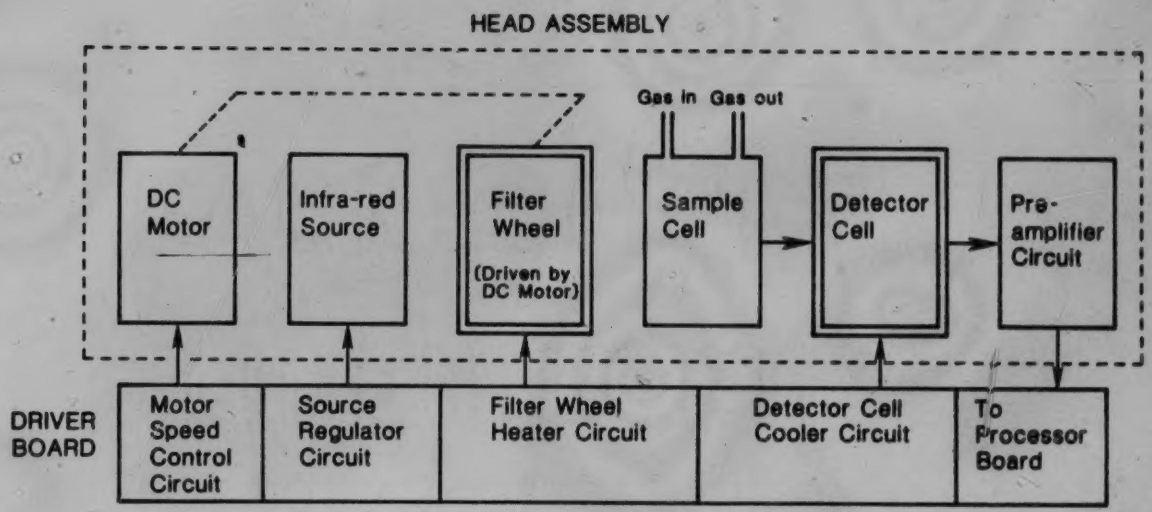

HEAD ASSEMBLY
Gas in
Gas out
DC Motor
Infra-red Source
Filter Wheel
(Driven by DC Motor)
Sample Cell
Detector Cell
Pre-amplifier Circuit
DRIVER BOARD
Motor Speed Control Circuit
Source Regulator Circuit
Filter Wheel Heater Circuit
Detector Cell Cooler Circuit
To Processor Board

Table 1-8

Systems Specifications of the Gould 9000IV Computerized Pulmonary Function Lab*

	Ranges	Resolution	Accuracy
Oxygen Analyzer	0 - 25%	.01%	± .10% oxygen
	0 - 50%	.02%	± .15% oxygen
	0 - 100%	.04%	± .20% oxygen
Carbon Dioxide Analyzer	0 - 10%	.01%	± 0.1% carbon dioxide
Spirometer	0 - 10 Liters	.01 Liter	± .025
	Inspiratory/Expiratory Flow measured to 20 liter/second	.01 LPS	± .10 LPS
Temperature	0 - 50°C	0.1°C	± 1° C

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* Adapted from: Gould Electronics Inc. Operator's Manual - Gould 9000IV Computerized Function Cart. Dayton, Onio, 1983:6.

metabolic EE of both spontaneously breathing and critically ill patients receiving mechanical ventilation. The ability to accurately measure these parameters becomes increasingly important as the F_IO_2 a patient receives is increased. Any source of error, such as flucuations in the F_IO_2 received by the patient, leaks within the ventilator-EE measurement system, or analyzer accuracy, will be progressively magnified as the F_IO_2 is increased (21).

(i) Fluctuations in F_I0_2 Value

Variations in hospital gas line pressures or minute-to-minute changes in oxygen blender output may cause fluctuations in the F_IO_2 delivered to the patient. Browning et al showed that delivery of a stable F_IO_2 to the patient throughout each breath and between breaths is essential to obtain accurate measurement of $\dot{V}O_2$ (20). They showed that internal blenders of ventilators do not provide an adequately stable F_IO_2 to ensure accurate $\dot{V}O_2$ measurement. This problem however, can be corrected by using an accurate external air-oxygen blender. Since Browning's work it has become common practice to use an external air-oxygen blender during metabolic EE studies in ventilated patients.

Ultman and Burzstein showed that as the F_IO_2 delivered to a patient is increased, the potential for error in $\dot{V}O_2$ measurement is correspondingly increased (21). This would be expected since most oxygen analyzers have the same limited absolute accuracy at any F_IO_2. Since the difference between inspired and expired oxygen concentration becomes narrower as the F_IO_2 is increased, a limited accuracy will produce a larger error when these smaller differences are measured. This can be illustrated by the following example. If the maximum error of the oxygen analyzer is ±0.0010 of the actual reading (±0.1% oxygen) over a range of 0 to 100% oxygen, the maximum error in $\dot{V}O_2$ obtained at an F_IO_2 of .2093, .4093, .6093 and .8093 would be ±15 ml/min, ±20 ml/min, ±31 ml/min, and ±63 ml/min respectively.

(ii) Leaks in the Ventilator-Metabolic Cart System

Errors in $\dot{V}O_2$ can occur if there is a leak in the system between where the F_IO_2 is measured and the F_IO_2 actually delivered to the patient. For example, if a mechanically ventilated patient is capable of drawing even minimal amounts of ambient air past the endotracheal cuff, the F_IO_2 measured proximal to this leak will not represent the true F_IO_2 received by the patient. As a result $\dot{V}O_2$ will be erroneously elevated. Similarly if there is a leak in the expiratory circuit of the patient and ambient air contaminates the expired gases, the F_EO_2 will be falsely low. Again the result is a falsely elevated $\dot{V}O_2$. In either situation, the error in $\dot{V}O_2$ is magnified as the F_IO_2 is increased.

McCamish et al. recently reported another possible source of error in measuring $\dot{V}O_2$ of mechanically ventilated patients (79). They studied $\dot{V}O_2$ and $\dot{V}CO_2$ of a 19 year old female who developed subcutaneous emphysema and bilateral pneumothoraces post-trauma necessitating placement of bilateral chest tubes. Continuous air leak from the chest tubes was accompanied by an extremely elevated $\dot{V}O_2$ and an unphysiological RQ value of approximately 0.4 to 0.5. The investigators suggest that oxygen leaks from the lungs in this situation produce a $\dot{V}O_2$ in excess of the actual volume consumed for metabolic purposes. Thus, accurate $\dot{V}O_2$ measurement cannot be made for mechanically ventilated patients who have chest tubes inserted unless accurate gas collection for measurement of volume, flow and concentration can be obtained from the tubes so that there are no leaks in the system.

Other sources of error in gas exchange measurements may be metabolic in nature. DuBois described a phenomenon of "auspumping" observed by the Germans, meaning pumping out or washing out of carbon dioxide by hyperventilation or over-ventilation of the lungs (39). Auspumping or carbon dioxide wash-out occurs when the patient's effective minute ventilation is acutely increased, either consciously or unconsciously. During this period of over ventilation, carbon dioxide expired per unit time is greatly in excess of the amount being produced per unit time. Therefore the resulting RQ will be erroneously high and any calculations based on $\dot{V}CO_2$ will be incorrect. The phenomenon of auspumping may be observed in a variety of situations where a patient acutely increases the depth and/or rate of respiration, such as in states of anxiety or acidosis (39).

Khambatta showed that in both animal and human studies, hypocapnic alkalosis can cause a considerable increase in $\dot{V}O_2$, up to 25% (60). Since hypocapnic alkalosis is associated with hyperventilation, increased $\dot{V}O_2$ is likely due, at least in part, to increased minute ventilation. In both situations, auspumping and hypocapnic alkalosis, the changes observed in gas exchange are short-lived. To ensure accurate results, metabolic measurement tests should be of a lengthy duration and/or tests should be repeated when these situations are suspected.

XII Factors Influencing Basal Metabolic Rate of Critically Ill Patients

Factors capable of influencing basal metabolic measurements in critically ill patients must be identified by performing metabolic measurements on this group of patients. These factors include age, sex and muscular development of the individual, diurnal variations, previous nutritional status, nutrient intake or infusion, previous muscular exertion or stimulus, and the severity of illness.

(i) Proportion of Lean Body Tissue

Benedict et al. (15) and many subsequent researchers (19,41,49,80) have shown that the basal metabolism of women is consistently lower than men of similiar height and weight. Similiarly it has been shown that athletes have higher metabolic rates than non-athletic individuals of similiar size (14). Also persons of the same sex, age and body weight but different height have different metabolic rates with the taller individual having a greater metabolic rate than the shorter individual (16). Benedict believed that the differences seen in all these instances could be explained by the proportion of active protoplasmic tissue, or lean body tissue, an individual has. That is, women have a greater proportion of inert fat than men. Consequently they have a lower porportion of active protoplasmic tissue, and a lower metabolic rate. Athletes have a larger porportion of lean body tissue than nonathletic individuals, as does a tall thin person in comparision to a shorter more stout individual of similiar body weight.

(ii) Previous Nutritional Status

Previous nutritional status is known to have a significant influence on basal metabolism. Starvation and chronic malnutrition are associated with large reductions in metabolic rate (3,4,72). Benedict performed a classical prolonged fasting study on a normal adult man and found basal metabolic rate fell 29% and body weight decreased 12.2 kg in 31 days (41). Metabolism fell a greater amount than could be attributed to loss of lean body tissue so the results suggested that some other mechanism(s) must have contributed to the decrease. Chronic malnutrition is associated with a gradual decline in basal metabolism (72). Askanazi et al. reported that the average EE of a group of depleted patients to be 21% below the predicted normal EE (4). Such a factor likely has an important influence on metabolic measurements of critically ill patients since many of these patients suffer from chronic malnutrition.

(iii) Ingestion of Nutrients

The ingestion or infusion of nutrients causes an increase in EE which gradually returns to normal as digestion and absorption is completed. This increase is commonly known as dietary induced thermogenesis. Gephart and DuBois in 1915 found that basal heat production of normal men increased approximately 12% over 3 to 6 hours following ingestion of 200 grams of carbohydrate or a casein meal containing 10.5 grams of nitrogen (48). Dietary-induced thermogenesis depends not only on the type and amount of nutrient infused (59,77,94) but also on the characteristics of the individual (4,112). In normal healthy volunteers, Zurlo et al. showed a 4.9±0.4% increase in EE during continuous infusion of enteral nutrition (112). Other researchers have shown the metabolic response to nutrient infusions to be different for normal, malnourished, and hypermetabolic individuals (4,94,113). Askanazi et al. found the metabolic response in malnourished patients to be different from hypermetabolic patients when amino acids were infused along with carbohydrate (4). In this study carbohydrate was infused in amounts exceeding measured EE by 35 to 125%. Nutrient infusion in malnourished patients resulted in a 32% increase in $\dot{V}CO_2$ and a 3% increase in $\dot{V}O_2$, whereas in hypermetabolic patients, the $\dot{V}CO_2$ production rose 56% and $\dot{V}O_2$ rose 29%. Roza et al. found that $\dot{V}O_2$ and $\dot{V}CO_2$ were significantly greater in malnourished patients than previously well nourished patients receiving parenteral nutritional support (97). In a recent study, Rodriguez et al. found that when intravenous carbohydrate was infused alone (no amino acids given) in amounts exceeding resting EE, only a small thermic effect was observed for both normal and traumatized patients (94). From these studies, it appears that nutrient infusions to critically ill patients will undoubtably influence metabolism. However the extent of this influence is not well understood.

(iv) Physical Activity

The after-effect of physical exercise on EE depends on the intensity, duration and type of exercise undertaken. Benedict and

Cathcart have shown that heat production remains elevated for several hours following completion of severe bicycle riding (11). Although this type of exercise will not be performed by a critically ill patient, it is quite possible that following a type of exercise such as weaning, EE may be elevated.

(v) Diurnal Variation

Diurnal variations in resting EE remains an area of controversy. Benedict reported the existence of three distinct metabolic planes; the lowest occurring while the patient is asleep, followed by a 14% increase when the subject is resting early in the morning and finally by a 22% increase over the sleeping value when the subject is measured resting late in the afternoon (16). Bailey et al. found that $\dot{V}O_2$ of normal men and women to have a cyclic pattern, with gradually increasing baselines (8). In opposition to these findings, Zurlo et al. found no diurnal variation between resting values obtained during the morning or late afternoon (113). Weissman et al. studied 3 critically ill patients for a 24 hour period and found resting EE to be 13±2% greater than when the patient was asleep (108). However no consistent diurnal pattern throughout the rest of the day was observed.

(vi) Analgesia and Sedatives

The administration of analgesic and sedatives to critically ill patients has been shown to alter metabolic rate. Rouby et al. (95) and Rodriquez et al. (93) found that the adminstration of 2 to 5mg of morphine sulfate per kilogram of patient's body weight per hour would cause an average decrease in $\dot{V}O_2$ of 21%. Rouby et al.

suggested that morphine may induce a genuine hemodynamic sedation that may be beneficial to the patient by helping to decrease the high metabolic rate induced by pain, anxiety, restlessness and hormonal stress (28). Damask et al. performed muscle biopsies on a group of normal men to determine metabolic response (28). The procedure itself was associated with a significant increase in $\dot{V}O_2$ and $\dot{V}CO_2$, presumably to be due to pain, which persisted for several minutes after the procedure was finished. Weissman et al. found a similiar response following various patient procedures in the ICU such as chest physiotherapy or repositioning (107). The $\dot{V}O_2$ and $\dot{V}CO_2$ often remained elevated above resting levels for 30 or more minutes. In view of these findings, it has been suggested that it may be possible to blunt the metabolic response seen in critical illness by providing the patient with adequate analgesia and/or sedation to minimize pain and anxiety. These studies suggest that administration of analgesics and sedatives should be considered when metabolic measurements are made in critically ill patients.

(vii) Severity of Illness

The last and probably most important factor influencing metabolic rate of critically ill patients is severity of illness and stage of illness being considered. As recognized by Cuthbertson the metabolic response to injury is characterized by two distinct phases; an early phase of "reduced vitality" where the patient is hypometabolic, and a later flow or ebb phase where the patient has become hypermetabolic (27). Metabolic measurements made during these different phases will provide variable results. Cuthbertson also observed that the metabolic response was proportional to the extent of injury sustained. From reviewing the literature on measured EE in critically ill patients it is apparent that metabolic rates are varied and inconsistent. This variability and inconsistency is likely due to a number factors such as anxiety, pain and infusion of nutrients which are difficult to control in the ICU setting. Severity of illness is likely the most important factor responsible for large intra-study and inter-study variability. The definition of critical illness may be viewed quite differently among investigators as evident from the studies reviewed. Some studies contain both spontaneously breathing and mechanically ventilated patients while other studies only include mechanically ventilated; some studies include burn, postsurgical traumatized, and septic patients while other studies only include postsurgical, nonseptic patients; some studies include both septic and nonseptic patients while other studies include only nonseptic patients.

When all of these groups are deemed to be representative of critically ill patients, it is not surprising measured EE is variable and unpredictable. In order to attempt to find appropriate stress factors for EE and more importantly, to evaluate the efficacy of nutritional support of critically ill patients, it is necessary to categorize and stratify the patient population. Various systems for scoring the severity of illness have evolved in the last few years such as the Trauma Score (22), the APACHE II score (68), the sepsis score (43) and TISS score (25). Use of such scoring systems will hopefully assist in more accurately documenting the severity of illness. By doing so, it may become possible to predict increases in EE associated with different types of degrees of critical illness. At present however, there does not appear to be any reliable substitution for actual measurement of EE in critically ill patients and adjust nutrient intake on an individual basis.

XIII The Purpose of the Thesis

At present there are no prospective clinical trials that show feeding mechanically ventilated critically ill patients reduces morbidity, decreases length of hospital stay or improves survival. However, before one can investigate the effects of nutrition, it is essential to have accurate measurement critera upon which to base the experiment. The amount of nutritional support provided to patients is commonly based on EE. The literature review firmly established that our present understanding of EE in critically ill patients is poor and that predictive equations commonly used to assess energy requirements of critically ill patients are inaccurate. The purpose of this thesis is therefore to accurately measure the daily EE of mechanically ventilated critically ill patients.

Until the last 10 years, the techniques available for performing these measurements were not suitable for accurate assessment of ventilated patients. Only recently have portable metabolic carts, capable of measuring $\dot{V}O_2$ and $\dot{V}CO_2$ to indirectly determine EE of critically ill patients, become accessible. The question then arises: are automated commercial systems capable of accurately measuring EE in mechanically ventilated critically ill patients?

The experimental work of Chapter 2 is a validation study of an automated portable metabolic cart. The two major questions to be answered in this chapter were: (1) can a portable metabolic cart be used to accurately measure $\dot{V}O_2$ and $\dot{V}CO_2$ of mechanically ventilated patients; and, (2) what are the accuracies and limitations of the of the system?

From the experimental work of Chapter 2, it was known that the Gould 9000IV Computerized Pulmonary Function Cart was capable of accurately measuring EE in mechanically ventilated patients who received an F_IO_2 of 0.60 or less. The next question to be answered was how does one determine daily EE? Usually daily energy requirements are based on the measurement of basal EE multiplied by a factor to account for daily activity. For ambulatory hospitalized patients, daily activity can range from 0 to 40% above measured basal EE, and consequently a mean activity factor of 20% is thought to be appropriate (45). Whether or not this was an appropriate factor for a nonambulatory mechanically ventilated ICU patient whose daily routine is markedly different from ambulatory hospitalized patients was not known. The purpose of the experimental work of Chapter 3 was therefore to determine: (1) whether or not a standard daily activity factor could be applied to the critically ill patient and (2) if so, what was the appropriate factor to accurately account for routine ICU activities?

During patient studies performed to answer the question of daily activity, it was observed on numerous occasions that the administration of analgesics and/or sedatives was often accompanied by a reduction in EE. This observation provided the experimental basis of Chapter 4 that has not been addressed previously. Does routine administration of analgesia affect the EE of critically ill patients?

The methods used, results and discussion of results of each of the three experiments performed are discussed in detail in the succeeding chapters. In summary, the purpose of each chapter were:

(1) to validate a compact metabolic cart capable of measuring EE in mechanically ventilated critically ill patients (Chapter 2);

(2) to determine twenty four hour energy expenditure in critically ill patients (Chapter 3);

(3) to determine the effect of routine administration of analgesia on the EE of critically ill patients (Chapter 4).

The efficacy of nutritional support of critically ill patients cannot be assessed until these issues have been adequately addressed.

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CHAPTER 2

VALIDATION OF A COMPACT SYSTEM FOR GAS EXCHANGE MEASUREMENT

I Introduction

Knowledge of EE and substrate utilization are important to the nutritional management of critically ill patients. Bedside measurement of EE, using indirect calorimetry to measure $\dot{V}O_2$ and $\dot{V}CO_2$ originated in 1908 when FG Benedict introduced the Benedict Portable Apparatus (10). Recently the development of automated compact systems which are easily portable and relatively simple to operate has sparked a resurgence of interest in measuring EE of hospitalized patients. All systems are composed of gas analyzers and a volume measurement system and most have automated features to handle calibration, testing and computation of data.

Other more traditional methods, such as a canopy system and the open circuit method using a Douglas bag or Tissot spirometer, have serious disadvantages when applied to the mechanically ventilated critically ill patient. Most canopy systems are static, requiring transport of the patient to the apparatus, and they are not adaptable to mechanically ventilated patients. The open circuit method can give rise to errors from loss of volume or contamination of the collected volume at each step of collection, storage and analysis. Also, only a single value is obtained from each expired gas collection and therefore multiple measurements must be made in an attempt to reduce the variability of random sampling. This becomes extremely laborious and time consuming.

Automated portable systems offer many advantages over traditional gas exchange measurement systems. Generally they are more compact and portable, capable of measuring gas exchange for long durations, and produce minute by minute data so that short-term changes in EE can be documented and any obvious errors can be noticed immediately. Like any measurement equipment, especially research equipment, one must ensure that the measurements made are accurate.

Gould Electronics Inc. (Medical Products Division, Dayton, Ohio) recently adapted the Gould 9000IV Computerized Pulmonary Function Cart for measurement of gas exchange in mechanically ventilated patients. Two characteristics of the 9000IV, direct expired volume measurement and automatic cycling between inspired and expired gas analysis suggested that this system might be suitable for studying critically ill patients. However, prior to clinical application, the system required validation. In this study, the accuracy of the Gould 9000IV was assessed in measuring $\dot{V}O_2$ and $\dot{V}CO_2$ at different levels of F_IO_2, tidal volume (V_T) and breathing frequency (f) commonly used to ventilate critically ill patients.

II Materials and Methods

(i) System Description

The Gould 9000IV is a portable automated system capable of measuring gas exchahge, calculating EE and substrate utilization in a mechanically ventilated patient. Its components include a paramagnetic oxygen analyzer, an infrared carbon dioxide analyzer, a dry rolling seal spirometer, a 32K random assess memory (RAM) computer with cathode ray tube (CRT) display of numeric and graphic data, and a reporter printer and plotter. A photograph of the Gould 9000IV is presented in Chapter 1, page 59.

The oxygen analyzer has a resolution of 0.01% and an accuracy of ± 0.10% over a range of 0 to 25% oxygen. Over the full scale of 0 to 100% oxygen, its resolution is 0.04% and its accuracy is ± .20%. The analyzer can be calibrated and verified using room air (F_I0_2 = .2093) for patients who are spontaneously breathing. For patient's receiving higher F_I0_2 values (greater than .2093), the analyzer can be calibrated with an oxygen concentration in the appropriate range.

The carbon dioxide analyzer has a resolution of 0.01% and an accuracy of ± 0.10% over a range of 0 to 10% carbon dioxide. The dry rolling seal spirometer measures f and V_T and has the capacity of 0 to 10 liters (L). Expired ventilation ($\dot{V}_E$) is derived from V_T and f with a resolution and accuracy of 0.01L and ± 0.025L respectively for V_T. The spirometer is calibrated with a 3L syringe. The volume measurements are automatically converted to standard temperature and pressure (STPD) using temperature from a thermister located in the spirometer and barometric pressure entered into the computer. The system has been described in detail in Chapter 1.

For use with mechanically ventilated patients, the system is connected to the expiratory port of the ventilator circuit and the patient's expired gas is collected in the spirometer. A sample of gas from the spirometer is pumped through a desiccation chamber containing Drierite^R and anhydrous calcium chloride and then to the carbon dioxide and oxygen analyzers for analysis. Inspired gas is sampled from the inspiratory side of the ventilatory circuit and pumped through a different desiccation chamber to the analyzers for analysis. A compressed gas driven solenoid valve switches between inspired and expired gas analysis every thirty seconds. The spirometer is continuously filled with the patient's expiratory gas and is rapidly emptied (dumped) by solenoid activation during an inspiratory cycle, following the collection of approximately 3L of expired gas. The computer continuously processes the spirometer and analyzer outputs, and stores and displays the data graphically and numerically on the CRT at one minute intervals. The system calculates gas exchange using standard equations (21).

The EE is calculated using the relationship derived from de V Weir (9) using Kleiber's tables (16):

$$\underset{\text{(kcal/day)}}{\text{EE}} = (3.796\ \underset{\text{(ml/min)}}{\dot{V}O_2} + 1.214\ \underset{\text{(ml/min)}}{\dot{V}CO_2})\ 1.44^{*}$$

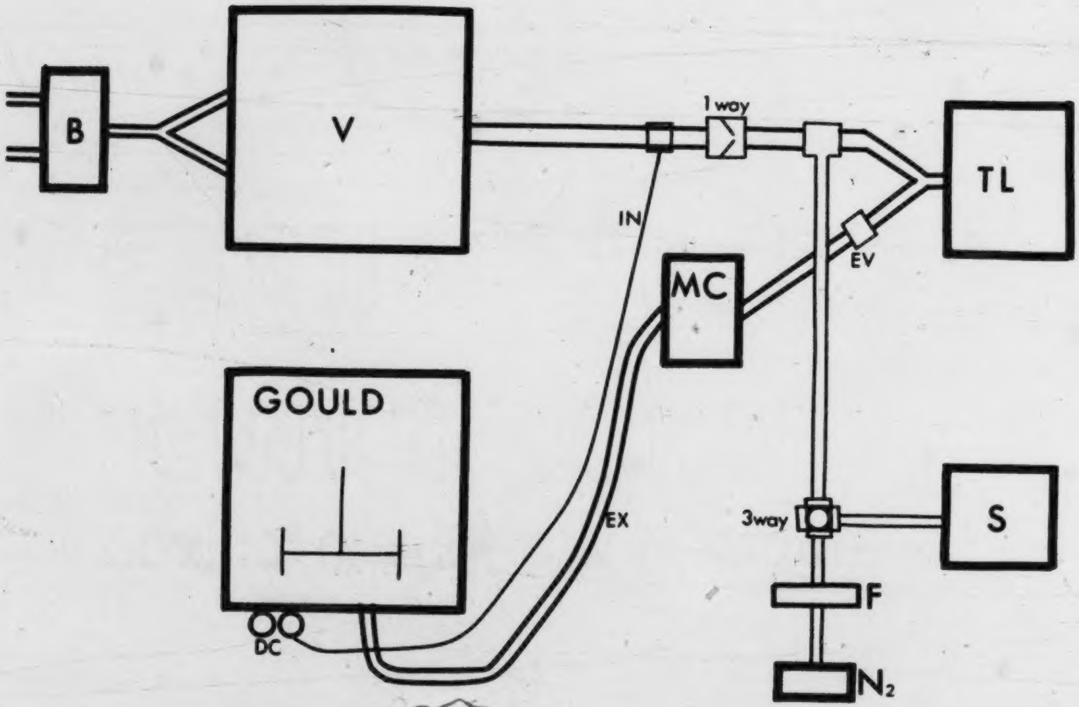
$$* \ \frac{1440\text{ min}}{\text{day}} \times \frac{\text{kcal}}{1000\text{ml}}$$

(ii) Validation Model

The Gould 9000IV was assessed by simulating various $\dot{V}O_2$ and $\dot{V}CO_2$ using a nitrogen and carbon dioxide infusion technique. The patient was simulated by a Vent-Aid test lung (Michigan Instruments Inc., Grand Rapids, Michigan), which was ventilated by a Bennett MA-2 ventilator (Puritan-Bennett Corp, Los Angeles, California). The system is diagramatically illustrated Figure 2-1. The inspired gas

FIGURE 2-1

Diagramatic representation of the Gould 9000IV validation system. An air-oxygen blender permitted alteration of F_IO_2 delivered by the ventilator to the test lung. The expired gas from the test lung passed through a mixing chamber prior to entering the Gould 9000IV's internal spirometer. Various flow rates of nitrogen could be introduced into the system to provide a difference in F_IO_2 and F_EO_2 appropriate to simulate various $\dot{V}O_2$'s.
B = air-oxygen blender; V = ventilator; 1 way - 1 way valve;
TL = test lung, IN = inspired sample tube; EV = expired valve;
MC = mixing chamber; S = water displacement spirometer;
EX = expired volume tube; F = flow meter; N_2 = nitrogen carbon dioxide source; DC = drying chamber.



sample was taken from the inspiratory tubing of the ventilator prior to a one-way valve. Nitrogen or carbon dioxide was added to the system downstream from the one-way valve proximal to the test lung. Dry gases were used, and the ventilator cascade humidifier was bypassed. Flows of nitrogen and carbon dioxide were controlled by a Matheson 601 or 603 flowmeter, with the flow rates measured before and after each trial with a water displacement spirometer (Godart Expirograph, I.A.I., New York, N.Y.). Although the test lung and dry-rolling seal spirometer functioned as mixing chambers, expired air leaving the test lung was further mixed in an additional mixing chamber prior to collection in the spirometer. The system was checked carefully at frequent intervals for leaks.

Three ventilator settings were tested: f=7 and V_T=600ml; f=10 and V_T=1000ml; and f=20 and V_T=1000ml. A range of F_IO_2 levels and nitrogen flows simulated a physiological range of $\dot{V}O_2$ exchange (Table 2-1). The 3 ranges of $\dot{V}O_2$ and 4 levels of F_IO_2 shown in Table 2-1 were tested at each of the 3 ventilator settings shown above. Also carbon dioxide flows of 200ml/min and 425ml/min were used to simulate $\dot{V}CO_2$ at the 3 ventilator setting. Each condition was repeated four times for a total of 144 $\dot{V}O_2$ and 24 $\dot{V}CO_2$ trials.

The analyzers were calibrated with room air and primary grade gases of 5.00% carbon dioxide, balance nitrogen and either 49.56% oxygen, balance nitrogen or 79.87% oxygen, balance nitrogen, depending on the F_IO_2.

Table 2-1

Approximate Nitrogen Flow Rates Used to Stimulate Various $\dot{V}O_2$ Values at Different F_IO_2 Values

$\dot{V}O_2$ (ml/min, STPD)	Nitrogen Flow (ml/min, STPD) F_IO_2 0.22	F_IO_2 0.40	F_IO_2 0.60	F_IO_2 0.80
200 - 300	950	350	200	70
400 - 450	1550	650	300	100
500 - 650	2000	875	450	175

The relationship used for calculating the stimulated $\dot{V}O_2$ and $\dot{V}CO_2$ was (32):

$$\dot{V}O_2 = \dot{V}N_2 \frac{F_IO_2}{1 - F_IO_2}$$

where $\dot{V}N_2$ = the nitrogen flow entering the test lung in ml/min (STPD) and $\dot{V}CO_2$ = carbon dioxide flow entering the test lung in mi/min (STPD).

(iii) Statistical Analysis

Descriptive statistics were performed on all data for each F_IO_2 level and ventilator setting. Pearson correlation coefficients were determined by relating the following variables, f, V_T, $\dot{V}_E$, F_IO_2 and nitrogen flow, to measured $\dot{V}O_2$ (27). Tests of significance were applied to determine statistically significant relationships using a level of $p<0.01$. This level was chosen to eliminate spurious correlations that had no physiological meaning and low correlation coefficients. Student's t-test for paired data was used to examine the difference between measured and calculated values of $\dot{V}O_2$ and $\dot{V}CO_2$ ($p<0.01$). The results from the four different F_IO_2 settings were subjected to a preliminary analysis of variance. For those F_IO_2 groups with a significant difference between measured and calculated $\dot{V}O_2$, the Scheffe multiple range technique was used to compare pairs of data (27).

III Results

(i) Oxygen Consumption

The accuracy of the 9000IV system was affected by the F_I0_2 level. As the F_I0_2 was increased, the relative error also increased as illustrated in Table 2-2. The mean difference between calculated and measured $\dot{V}0_2$ at each F_I0_2 value was statistically significant.

Using Pearson correlation coefficients, no statistically significant relationships were found between $\dot{V}_E$, f, or V_T and measured or calculated $\dot{V}0_2$. However, the correlation between measured and calculated $\dot{V}0_2$ for all trials and for each F_I0_2 value was highly significant (Figure 2-2).

One way analysis of variance showed a significant difference between measured and calculated $\dot{V}0_2$ ($\dot{V}0_2$ diff) ($F=167.5$, $p<0.001$) and permitted use of the Scheffe technique to compare pairs of data. The $\dot{V}0_2$ diff increased significantly when the F_I0_2 value was increased from 0.40 to 0.60 and from 0.60 to 0.80. The $\dot{V}0_2$ diff was not significantly different between the F_I0_2 value of 0.22 and 0.40. Mean $\dot{V}0_2$ diff at F_I0_2 values of 0.22, 0.40, 0.60 and 0.80 was 8, 15, 24, and 65 ml/min respectively. The overall relative errors of measured $\dot{V}0_2$ were 2.6%, 3.5%, 5.9% and 16.9% at F_I0_2 values of 0.22, 0.40, 0.60. and 0.80 respectively.

(ii) Carbon Dioxide Production

Using Student's paired t-test, there was no significant difference between measured and calculated $\dot{V}C0_2$ when the average of all trials, or when individual ventilator settings were considered.

Tidal volume, f and $\dot{V}_E$ showed no significant correlation ($p<0.01$) with either measured or calculated $\dot{V}C0_2$. There was a

Table 2-2

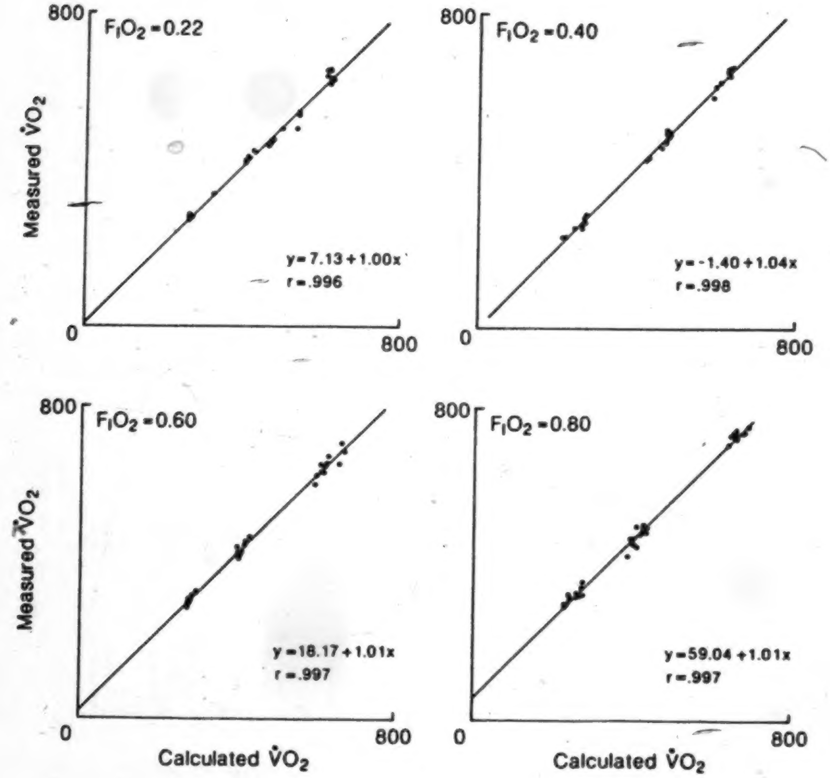
Relative Error of the Gould 9000 IV at Different F_IO_2 Values

F_IO_2	$\dot{V}O_2$ (mean ± SEM, ml/min) calculated	measured	p-Value	Relative Error* (± SEM)
0.22 (n=36)	440.4±22.8	447.5±22.9	$p<.002$	2.6±0.3%
0.40 (n=36)	446.8±26.2	461.6±27.2	$p<.001$	3.5±0.4%
0.60 (n=36)	438.2±24.1	462.0±24.5	$p<.001$	5.9±0.5%
0.80 (n=144)	442.5±12.7	509.5±29.1	$p<.001$	16.9±0.6%

* $$\text{Relative error} = \frac{\text{measured } \dot{V}O_2 - \text{calculated } \dot{V}O_2}{\text{calculated } \dot{V}O_2} \times 100$$

FIGURE 2-2

The correlation between measured $\dot{V}0_2$ and calculated $\dot{V}0_2$ at the 4 F_I0_2 values tested.



highly significant relationship between all measured and calculated $\dot{V}CO_2$ values ($r=0.998$, $p<0.001$). The overall relative error was 2.6±0.5% (Table 2-3).

IV Discussion

The capability of accurate and easy measurement of EE in critically ill patients is a significant advance. This is particularly so for this group of patients, since there appears to be a "fine-line" for energy balance as both underfeeding and overfeeding can be associated with complications. Delivery of inadequate energy has been associated with decreased survival rate (5,18), respiratory muscle wasting (2,15), poor wound healing (13) and depressed immunocompetency (20); whereas overfeeding critically ill patients can result in large elevations in $\dot{V}O_2$ and $\dot{V}CO_2$, thereby stressing both cardiovascular and respiratory systems (3,23,29). Also, excessive parenteral infusion of carbohydrate (14,27) and lipid (17) have been implicated as important etiological factors in the development of fatty infiltration of the liver. In addition to clinical importance, excess nutrient infusion of parenteral nutrition is expensive and therefore monitoring of EE to prevent overfeeding can be of very practical importance.

Several investigators (4,5,11,19,22,24,31) have shown that predicted EE based on equations such as Harris and Benedict (12), Rutten (25) and Curreri (7) correlate poorly with measured EE in malnourished, postoperative, septic and burned patients. The degree of hypermetabolism found during critical illness has recently become

Table 2-3

Relationship Between Calculated and Measured $\dot{V}CO_2$

Ventilator setting $f; V_T$ (L)	$\dot{V}CO_2$ calculated ±SEM (ml/min)	$\dot{V}CO_2$ measured ±SEM (ml/min)	Significance	Relative error%* ±SEM
20; 1.0 n = 8	310.1±42.2**	322.6±45.4	$p = 0.020$	3.6±1.0
10; 1.0 n = 8	313.4±42.5**	317.0±41.6	$p = 0.060$	1.7±0.8
7; 0.6 n = 4	201.0±1.0***	196.3±1.6	$p = 0.125$	2.4±1.2
Total	289.6±25.1	295.1±26.2	$p = 0.030$	2.6±0.5

*

$$\text{relative error } \% = \frac{\text{measured } \dot{V}CO_2 - \text{calculated } \dot{V}CO_2}{\text{calculated } \dot{V}CO_2} \times 100$$

** $\dot{V}CO_2$ calculated and measured are averaged from both CO_2 flows of 200ml/min and 425ml/min

*** $\dot{V}CO_2$ calculated and measured are averaged from CO_2 flow of 200ml/min only

n = number of trials

a very controversial issue. These studies emphasize the need for an accurate method for the determination of EE.

The 9000IV was adapted for the measurement of gas exchange in mechanically ventilated patients. It is equipped with automated inspired gas sampling and a pressure damping coil to help prevent ventilator pressure from affecting the analyzers. The manufacturer states an accuracy of ±5% for the measured values for $\dot{V}O_2$ and $\dot{V}CO_2$ but fails to state the F_IO_2 range for which this statement is valid.

On initial assessment of the system, large errors were found, reaching 43% of the calculated $\dot{V}O_2$ at an F_IO_2 value of 0.60. This large error was found to be due, at least in part, to rebound of the spirometer dump mechanism at the end of the dump cycle, causing room air entrainment before the dump port closed. Room air contaminated the expired air, resulting in the system reading a factitiously low F_EO_2 and therefore calculating an erroneously high $\dot{V}O_2$. As the F_IO_2 value was increased, the contamination by room air had a more pronounced effect. The problem was corrected by the addition of a large dead space, consisting of 3 meters of household dryer vent hose to the spirometer dump port. Expired air in the dead space that had just been dumped from the spirometer was then entrained instead of room air.

The pressure of the compressed gas source which drives the solenoids that control the dump mechanism was increased to determine if this would eliminate the room air contamination. To ensure a constant and higher driving pressure for the solenoids, the usual wall source of compressed oxygen (45-50 PSI) was switched to a tank of oxygen regulated at the manufacturer's recommendation of 61 PSI. This system was tested at an F_IO_2 value of 0.80 and the error remained at the high level previously found (greater than 60%). The accuracy improved only with the addition in the dead space.

Accuracy of the 9000IV with the dead space adaptation improved to 5.9% and 16.9% at F_IO_2 values of 0.60 and 0.80 respectively. However, there continued to be a systematic error as $\dot{V}O_2$ was consistently overestimated and the error increased as the F_IO_2 value was increased (Table 2-2). The magnitude of the error became significantly greater at F_IO_2 values of 0.60 and 0.80. The systematic error likely arises from continued, although lessened, room air contamination of the expired gas despite the dead space adaptation. Highly significant correlations between measured and calculated $\dot{V}O_2$ support this suggestion as the error observed is not random in nature.

It is not surprising that the error is very high at a high F_IO_2. At high F_IO_2 values, $\dot{V}O_2$ is calculated from the difference between two similar numbers. The difference between F_EO_2 and F_IO_2 becomes smaller in proportion to their absolute values and approaches both the resolution of the analyzer and the stability of the F_IO_2 value delivered by the oxygen blender. The Gould 9000IV oxygen analyzer has a resolution of 0.0004 at full scale. Therefore at an F_IO_2 value of 0.80, a typical $\dot{V}O_2$ of 250ml/min can result in a difference between F_IO_2 and F_EO_2 of only 0.0070. Theoretically, the maximum accuracy of the Gould 9000IV is 5.7% (0.0004/0.0070 x 100) at an F_IO_2 value of 0.80. Any leak or contamination within the ventilator circuit or the Gould system will have a proportionally larger effect on the small differences measured at high oxygen levels. The error was magnified from the theoretical 5.7% to an actual 16.9% at an F_IO_2 value of 0.80, probably due to room air contamination of spirometer gas. Without adding nitrogen to the system, the test-lung system was tested for leaks by removing the expired sample tubing from the spirometer and placing it in many different locations on the expiratory side of the test lung. If no leaks occurred F_IO_2 should equal F_EO_2. At all locations checked, both F_IO_2 and F_EO_2 were the same or fluctuated randomly within a narrow range therefore giving rise to $\dot{V}O_2$ and $\dot{V}CO_2$ values of ±3ml/min. However, again without adding nitrogen, the expired gas sampled from the spirometer was found to be consistently lower in oxygen concentration than the inspired gas. The difference between F_IO_2 and F_EO_2 as measured by the Gould 9000IV when no nitrogen was added explained the large error in observed $\dot{V}O_2$ observed. The contamination appears to result in a systematic type of error with a highly significant correlation between measured and calculated $\dot{V}O_2$ as suggested by linear regression equations with slopes very close to 1.0 (Figure 2-2).

Accurate carbon dioxide production is easier to measure. The accuracy of ±2.6% fell within the manufacturer's specification of ±5%. No systematic error was found (ie no statistically signficant difference between measured and calculated $\dot{V}CO_2$), and correlation between measured and calculated $\dot{V}CO_2$ was highly significant. Four trials at a $\dot{V}_E$ of 5L/min and CO_2 flow of 400ml/min STPD were not included in the statistical analysis. The expected $\dot{V}CO_2$ of 400ml/min could not be measured as it surpassed the analyzer capabilities at this low $\dot{V}_E$. This is not relevant, however as it is physiologically unlikely for such a large $\dot{V}CO_2$ to be matched to such a low $\dot{V}_E$. Room air contamination did not give the same systematic error in $\dot{V}CO_2$ measurement as it did in $\dot{V}O_2$. The F_ECO_2, with a range from approximately 0.01 (carbon dioxide flow = 200ml/min; $\dot{V}_E$ = 20L/min) to 0.06 (carbon dioxide flow = 425ml/min, $\dot{V}_E$ = 10L/min) was diluted with room air with an F_ICO_2 close to zero. Because these two concentrations are so close in value, the effect is less pronounced than when F_EO_2 of 0.80 is diluted with room air with an F_IO_2 of 0.21. Room air contamination may lower F_ECO_2 slightly causing a small systematic error which is buried in the random error.

Accuracy of this, and other validation studies (1,8,32) is limited by the accuracy in delivery of nitrogen and carbon dioxide. Flow of nitrogen and carbon dioxide was checked by diverting flow to a water displacement spirometer before and after each trial. Values were within 1 to 2ml/min each time, or from 0.05% to 1.0% of the actual flow. During the tests the flows were considered to be the same as those into the spirometer since the slight pressures against which the gas was being delivered had no measurable effect on flow. Also, the correlation coefficients show that measured $\dot{V}O_2$ was not affected by V_T, which by necessity, changes pressure in the test lung into which the nitrogen and carbon dioxide was flowing.

Another limitation to accurate $\dot{V}0_2$ measurements is the stability of the F_I0_2 value being delivered. Fluctuations in F_I0_2 levels with the internal blenders of various ventilators can be reduced by the use of a separate external blender (6). A Bird blender (3M Corp., Palm Springs, Ca) was used to deliver a reasonably stable ($F_I0_2 \pm .0004$) air-oxygen mixture to the ventilator. However, small fluctuations in F_I0_2 value still occurred thus emphasizing the need for frequent analysis of F_I0_2 level.

Although we studied a range of $\dot{V}_E$, f and V_T was studied at which various $\dot{V}0_2$ and $\dot{V}C0_2$ were measured, not all ICU conditions were simulated in this study. High airway pressures, intermittent mandatory ventilation or positive-end expiratory pressure were not mimicked. Frequent cart movement, a potential source of destabilization occurring in an ICU setting, was minimized in this series of tests.

V Conclusion

It is concluded that the Gould 9000IV with a dead space modification has an acceptable error in gas exchange measurement under controlled laboratory conditions for an F_I0_2 value of 0.60 or less. The magnitude of the error was similar to other automated systems (5). As a clinical tool, its applications and potential benefits justify continued investigation to determine its accuracy in the clinical setting.

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CHAPTER 3

TWENTY FOUR HOUR ENERGY EXPENDITURE IN CRITICALLY ILL PATIENTS

I Introduction

The increased availability of mobile systems capable of measuring $\dot{V}O_2$ and $\dot{V}CO_2$ has resulted in numerous reports on the EE of various patient populations, such as burn (26,29), post-neurosurgical (5,6,7), and critically ill patients (22,31,32). Measurement of resting EE alone or with the addition of an arbitrary "activity factor" is often used to dictate the patient's daily caloric intake. For the ambulatory hospitalized patient the contribution of daily activities to total EE has been documented to be approximately 20% above resting EE (12,18). However, the activity factor for critically ill patients has not been satisfactorily determined.

Total EE in nonambulatory critically ill patients might be expected to be quite different from resting EE + 20% as Weissman et al. showed in three critically ill patients that total EE averaged only 5% above resting EE (31). However, due to the small number of patients studied further investigation of EE was believed to be justified. Cumulative 24 hour EE therefore was measured in 10 mechanically ventilated critically ill patients. From this information an activity factor has been determined which can be applied to this group of patients by comparing measured resting EE to available predicted values based on the Harris-Benedict equation (13).

II Materials and Methods

(i) Patient Description

Ten mechanically ventilated critically ill patients patients

(8 males, 2 females) admitted to the General Systems ICU at the University of Alberta Hospitals were studied. Clinical status of the patients was defined by the APACHE II scoring system (16) and the influence of sepsis was assessed using the sepsis score (11). Patient age, diagnosis, APACHE II and sepsis score, study day post-ICU admission, F_I0_2 and positive end-expiratory pressure (PEEP) used during the study and outcome are presented in Table 3-1.

(ii) System Description

A Gould 9000IV Computerized Pulmonary Function Cart (Medical Products Division, Dayton, Ohio) was used to determine $\dot{V}0_2$ and $\dot{V}C0_2$ over a 24 hour period. This metabolic cart was specifically designed to measure gas exchange in mechanically ventilated patients. The 9000IV includes a paramagnetic 0_2 analyser (accuracy of ± 0.2% up to 100% 0_2), an infrared $C0_2$ analyser (accuracy of ± 0.1% up to 10% $C0_2$) and a dry rolling seal spirometer which derives expired minute ventilation ($\dot{V}_E$) from breathing frequency (f) and tidal volume (V_T) (accuracy of ± 0.01L). This particular 9000IV has been previously validated at this institution (10) for accuracy in $\dot{V}0_2$ and $\dot{V}C0_2$ measurements at various F_I0_2 values (Chapter 2). The F_I0_2 had a statistically significant effect on the accuracy of measuring $\dot{V}0_2$ with the error averaging 2.6%, 3.5%, 5.9%, and 16.9% for F_I0_2 values of 0.22, 0.40, 0.60 and 0.80, respectively. Patients ventilated with an F_I0_2 greater than 0.60 were not studied due to the limited accuracy of $\dot{V}0_2$ measurements at high F_I0_2 values.

TABLE 3-1
Patient Description, Severity of Illness and Outcome (mean ± SD)

Sex and Age of Subject in Years	Clinical Description*	Admission APACHE II Score	Sepsis Score	Study Day Post-ICU Admission	PEEP (cmH_2O)	F_IO_2	Outcome**
M, 70	COPD, postop aortic valve replacement, postop MI, ARDS septicemia, pneumonia, RF	31	21	9	12.5	0.50	D
M, 61	Cecal volvulus, postop hemicolectomy, with ileostomy and transverse mucous fistula, grand mal seizure, aspiration pneumonia, ARDS, RF	24	11	17	5.0	0.35	D
M, 79	Left pulmonary abscess, COPD, bleeding gastric ulcer, postop vagotomy, pylroplasty, gastrostomy, jejunostomy, septicemia	34	23	5	7.5	0.40	D
M, 73	Lower GI bleed, repair of ventral hernia, sequential resection of splenic flexure of colon resection	25	14	5	5.0	0.35	S
M, 64	Trauma - kicked in abdomen by steer, small bowel transection, postop laparotomy and relaparotomy for intra-abdominal sepsis, decompression of small bowel, gastrostomy, jejunostomy	22	10	5	5.0	0.45	S

Continued on page 113

(Continuation of TABLE 3-1)

M, 27	MVA - facial laceration and smash, basal skull fracture, multiple rib fractures, liver laceration, ceccal contusion	16	0	5	5.0	0.30	S
M, 68	MVA - postop laparotomy, scalp laceration, multiple rib fractures, hemothorax, hemoperfusion, fractured femur	12	2	7	5.0	0.35	D
M, 72	Bowel infarction, postop laparotomy, resection of large portion of ischemic small bowel	12	5	8	10.0	0.45	S
F, 62	Postop coronary artery bypass, mediastinitis, septicemia, shock, ARDS, pneumonia	23	23	4	7.5	0.45	D
F, 49	Acute myelogenous leukemia, post-chemotherapy treatment, septicemia	28	17	5	5.0	0.35	S
63±15		23±7	13±8	7±4	6.8±2.6	0.40±0.06	

* COPD - chronic obstructive pulmonary disease; MI - myocardial infarction; ARDS - adult respiratory distress syndrome; GI - gastrointestinal; MVA - motor vehicle accident; RF - renal failure

** D - died; S - survived

(iii) Patient Studies

For patient studies, the 9000IV was connected to the expiratory port of the patient's ventilatory circuit. Expired gas from the patient was collected in the dry rolling seal spirometer. After collecting approximately 3 liters, the spirometer rapidly empties during an inspiratory cycle. The spirometer acted as a mixing chamber and expired 0_2 and $C0_2$ were obtained from this source. To measure F_I0_2, a sample of inspired gas was obtained from tubing connected to the inspiratory limb of the ventilatory circuit. The 9000IV alternates between inspired and expired analyses every 30 seconds. The system provides indices of gas exchange every minute using standard equations (23). Measured EE is calculated using the relationship derived from de V Weir (8) using Kleiber's tables (15):

$$\underset{\text{(kcal/day)}}{\text{EE}} = (3.796 \underset{\text{(ml/min)}}{\dot{V}0_2} + 1.214 \underset{\text{(ml/min)}}{\dot{V}C0_2})\ 1.44$$

$$* \frac{1440 \text{ min}}{\text{day}} \times \frac{\text{kcal}}{1000 \text{ ml}}$$

The duration of each test was approximately 1 hour. Following each test the analysers were recalibrated, the drying agents in the analyzer circuit were changed, and the patient's ventilatory circuit was emptied of any accumulated water. The mean ± S.D. number of hours each patient was tested during the 24 hour study was 20.75 ± 0.75 hrs.

Prior to and at the end of each 24 hour patient study, the 9000IV was validated by connecting it to an in vitro system consisting of a Vent Aid test lung (Michigan Instruments Inc., Grand Rapids, Michigan) which was ventilated by a Bennett MA-2 ventilator (Puritan-Bennett Corp., Los Angeles, California). The f, V_T, peak airway pressure and F_I0_2 of each patient studied were used for the in vitro test. To provide a constant F_I0_2 (4), the air and oxygen delivered to the ventilator was mixed by a single air-oxygen blender (Siemens-Elema, Sweden). This blender was also used for all patients studied. Blenderized air-oxygen at the desired F_I0_2 was ventilated through the ventilator-test lung system and into the 9000IV for a half hour period. Since no 0_2 was consumed by or $C0_2$ added to this system, $\dot{V}0_2$ and $\dot{V}C0_2$ should have been zero if there were no leaks or effects of pressure. For all ventilator settings and F_I0_2 values used for patient studies, the measured $\dot{V}0_2$ and $\dot{V}C0_2$ were ± 3 ml/min.

The activity state of each patient was continuously observed and recorded during the 24 hour study. "Rest" was defined as a patient lying motionless and apparently comfortable with eyes open and/or closed, following 30 minutes of post-event rest. "Post-event rest" was defined as the patient lying motionless and apparently comfortable with eyes open or closed following some activity such as repositioning or chest physiotherapy. No attempt was made to separate sleep from resting with eyes closed. "Agitation and/or restlessness" was defined as a patient appearing uncomfortable, grimacing and/or moving body limbs without purpose. Each activity and the amount of time engaged in it was recorded.

Because a major aim of the study was to measure EE during routine ICU care, no attempt was made to standardize nutrient intake or administration of analgesics and sedation. However, the amount and time that analgesics and sedation were given during the 24 hour period were recorded. One patient did not receive any analgesia or sedation. For the remaining 9 patients, an average of 57±43mg of morphine was administered (range = 13 to 161 mg) alone or in combination with diazepam. Patient 5 received a constant morphine infusion, and all other patients received analgesia and sedation on an "as necessary" basis.

All infusion rates of nutrient solutions (enteral or parenteral) remained constant during the 24 hour period prior to and during all patient studies. Change in EE related to varying nutrient intake was therefore not expected. Actual macronutrient intake for all patients is presented in Table 3-2. Predicted EE was determined by the Harris-Benedict equation, based on the patient's height, usual body weight and age (13):

$$\text{Males} = 66.47 + 13.75W + 5.0H - 6.76A$$

$$\text{Females} = 655.10 + 9.56W + 1.85H - 4.68A;\ \text{where,}$$

W = weight in kilograms, H = height in centimeters,

A = age in years.

(iv) Statistical Analysis

Descriptive statistics (mean and standard deviation) were determined for each variable at each time period (28). Student's t-test for paired data was used to evaluate differences between resting EE, post-event resting EE and the EE associated with various

TABLE 3-2

Patient Nutrient Intake During the 24 Hour EE Study (mean±SD)

Patient	Types of Nutritional Support	Total Energy (kcal)	Components of Carbohydrate (gm)	Nutrient Protein (gm)	Intake Fat (gm)
1	enteral	2400	300	84	96
2	intravenous dextrose	264	78	0	0
3	peripheral parenteral	2130	240	90	106
4	peripheral parenteral	2248	264	99	106
5	peripheral parenteral	1895	192	72	106
6	peripheral parenteral	1895	192	72	106
7	peripheral parenteral	2130	240	90	106
8	central parenteral	1815	269	105	53
9	intravenous dextrose	490	144	0	0
10	peripheral parentral	1895	192	72	106
		1716±731	211±66	68±38	79±44

activities. Paired Student's t-test was also used to evaluate the difference between total EE and resting EE as well as resting EE and predicted EE. Pearson's correlation coefficient was used to evaluate the relationship between admission APACHE II score and percentage that resting EE was above predicted EE. A probability level of less than 5% was considered to be statistically significant.

III Results

The age of patients was 63±15 years and they were studied 7±4 days after admission to the ICU (Table 3-1). Admission APACHE II scores were 23±7, indicating that these patients were severely ill. A 50% mortality rate was observed during the post-study ICU course. The percent of measured resting EE above predicted EE correlated significantly with the admission APACHE II score ($r=0.64$, $p<0.02$). The average sepsis score on the day of the study was 13±8 and the score exceeded 20 in three patients.

Predicted EE, resting EE and total EE for all patients are presented in Table 3-3. Predicted EE was 1501±202 kcal/day. The measured resting EE was 2186±343 kcal/day or 47.3±22.3% above the predicted EE. Resting EE was signficantly greater than predicted EE for all patients ($p<0.01$). The total EE for the 10 patients was 2342±371 kcal/day or 6.9±2.6% (range 1.4 to 10.6%) above the resting EE ($p<0.01$).

Actual energy intake, tctal EE and resulting energy balance for the 24 hour study period is presented in Figure 3-1. The daily caloric intake was 1716±731 kcal/day. The total EE was 2242±371

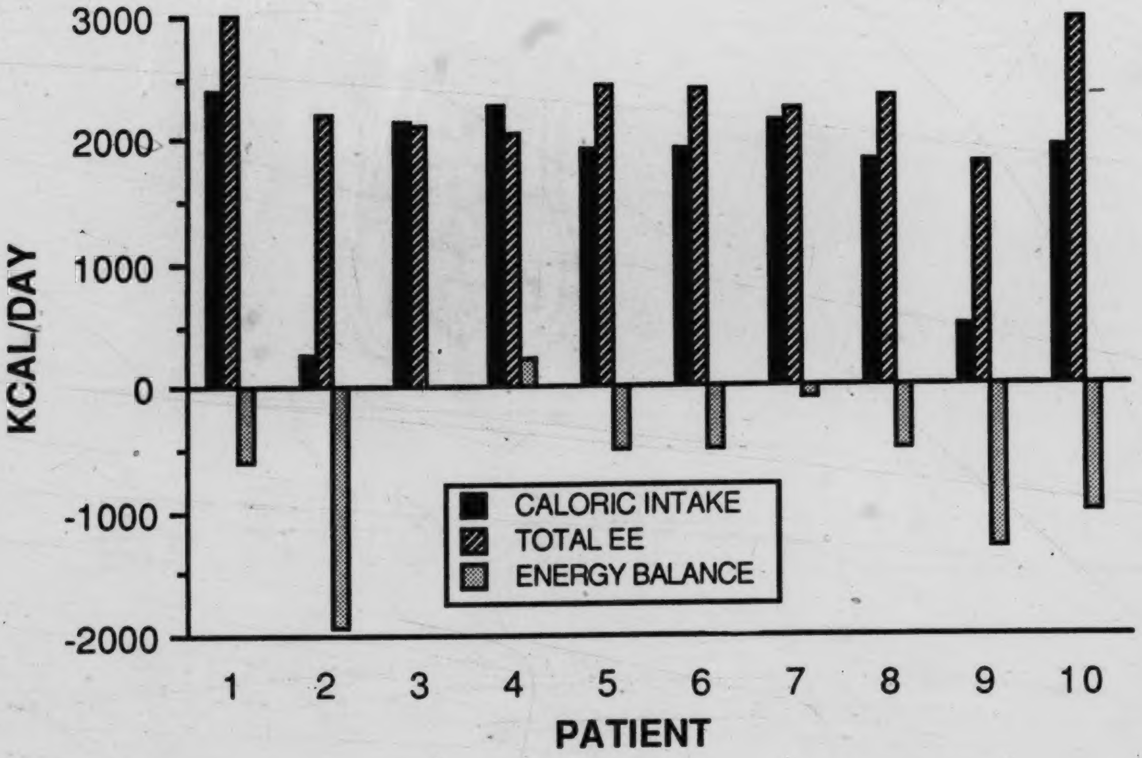
TABLE 3-3

Resting and Total Energy Expenditure (mean ± SD)

Patient	Predicted EE	Measured Resting EE	% Measured Resting EE Above Predicted EE	Measured Total EE	% Total EE Above Resting EE
1	1589	2751	73.1	2997	9.0
2	1459	2177	49.2	2208	1.4
3	1085	1980	82.5	2115	6.8
4	1567	1908	21.8	2040	6.9
5	1770	2178	23.1	2408	10.6
6	1647	2175	32.0	2394	10.0
7	1423	2113	48.5	2234	5.7
8	1630	2168	33.0	2316	6.8
9	1260	1706	35.4	1793	6.1
10	1582	2761	74.5	2915	5.6
	1501±202	2192±334	47.3±22.3	2342±371	6.8±2.7

FIGURE 3-1

Total energy expenditure, caloric intake and energy balance in each of the 10 patients over the 24 hour study period.



kcal/day and therefore the resulting energy balance was negative (-526±648 kcal/day). Only patients 3 and 4 received adequate calories to meet or exceed total EE.

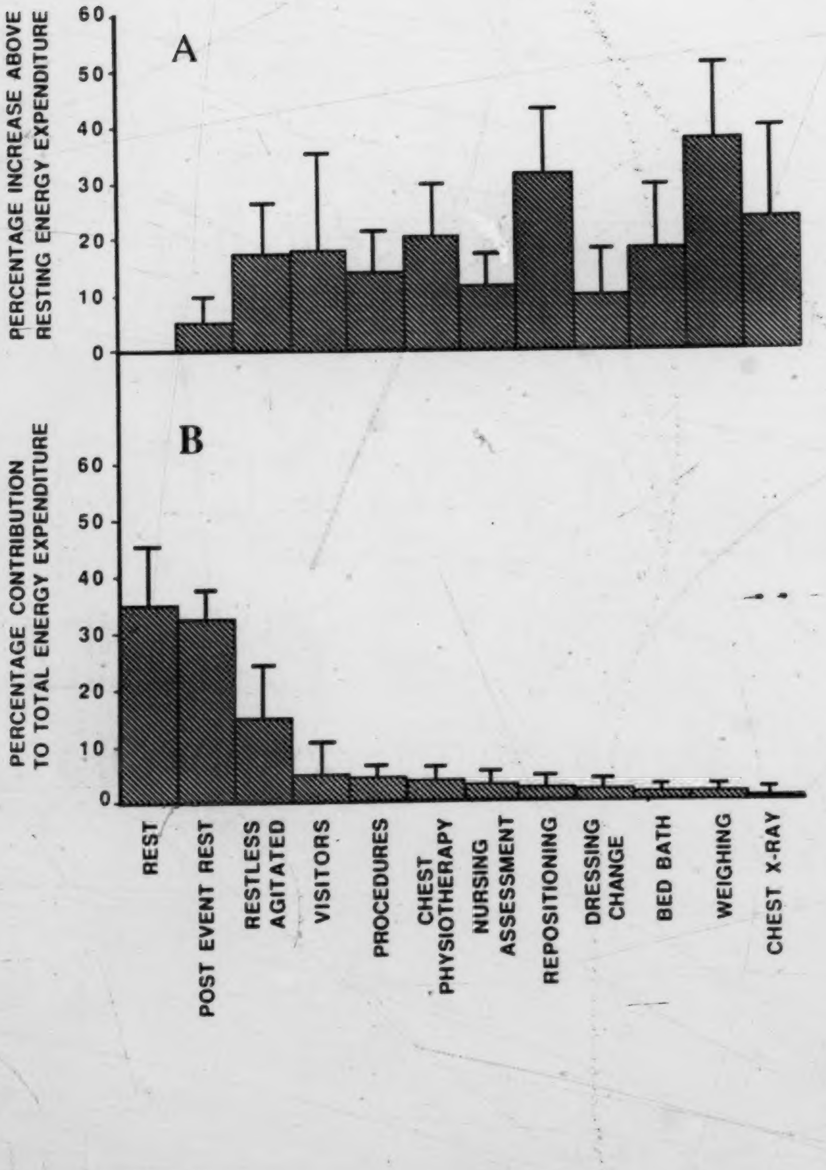
The percentage increase in post-event resting EE and various activities above the resting EE are presented in Figure 3-2A. During the 30 minutes after an activity (post-event resting EE), EE was higher than resting EE by an average of 5.8±4.3%. This increase was significant for 7 of the 10 patients ($p<0.05$), however, it was not significantly increased for patients 1, 2 and 10. Activities such as weighing on a bed scale, repositioning, chest physiotherapy, bed bath, dressing change and chest x-ray were associated with increases in EE of 36±12%, 31±11%, 20±10%, 10±9%, and 22±16% respectively. The state of agitation and/or restlessness was associated with a 18±8% increase in EE above resting EE.

Although certain activities caused considerable elevations in EE, due to their short duration their actual contribution to the total daily EE was small. Figure 3-2B shows the contribution to the total EE of the two types of defined rest and the various activity states. Following rest, the state of agitation and restlessness was the greatest contributor (13.7%) to the total EE.

Average $\dot{V}O_2$ and $\dot{V}CO_2$ observed during rest were 320±47ml/min and 254±45ml/min, respectively. Percentage increase in $\dot{V}O_2$ and $\dot{V}CO_2$ during post-event rest were 5.7±4.7% and 5.1±5.0%, respectively. These increases correspond closely to the percentage increase seen in post-event resting EE above resting EE. This was also found for the various activities, $\dot{V}O_2$ and $\dot{V}CO_2$ were

FIGURE 3-2

(A) The percentage increase above the resting energy expenditure associated with various ICU activities.
(B) The contribution of activities to the total energy expenditure. Values are expressed as mean ± SD.



associated with percentage rises similar to the values of EE above resting levels.

The mean resting respiratory quotient (RQ) for patients receiving nutritional support (n=8) was 0.82±0.02. The mean resting RQ values for patients 2 and 9 who received only intravenous dextrose was 0.73±0.01 and 0.71±0.01, respectively. In both cases, small amounts of dextrose were received as the total nutritional support, and therefore, the low RQ observed is likely a result of endogenous fat oxidation. During activities the average RQ values often decreased from the resting level. In no instance were these decreases statistically significant.

IV Discussion

Recent studies have shown that critically ill patients are not as "hypermetabolic" and do not have the large increases in EE that were previously described for other patients (18,33). Baker et al. found that in a group of mechanically ventilated respiratory care ICU patients, the resting EE was only 4.6% above predicted EE using the Harris-Benedict equation (3). Weissman et al. reported resting EE to be 3.8% above predicted EE in 40 postoperative polytrauma and surgical patients receiving mechanical ventilation (32). Their patients did not receive nutritional support or sedation at the time of the study. Similarly, Mann et al. found that in 50 acutely ill patients, some mechanically ventilated and others not, the measured resting EE was 15% above the predicted EE (22).

For the group of critically ill patients in this study, resting

EE was considerably higher (47.3±22.3% above predicted EE) than values recently reported. There are likely several factors contributing to the discrepancy in resting EE of a very large and variable group called "critically ill patients". Factors such as feeding, sedation and/or analgesia, and degree of illness and stress will affect metabolic rate. As suggested by Weissman et al., finding an initial reference state from which to calculate the EE for the critically ill patients is a difficult task (30).

During the EE studies, 7 patients received parenteral nutritional support, 1 received enteral nutritional support and 2 were given intravenous dextrose only. This undoubtedly influenced the resting EE due to the specific dynamic action of nutrient intake. Although both type and amount of nutrient infused influence the thermic response, the contribution of nutrient infusion to EE is not well defined (14,21). Elywn et al. reported that normal diets or constant infusion of intravenous nutrients both result in a 10% increase in basal metabolic rate (12). However, Askanazi et al. found that feeding critically ill patients with intravenous dextrose in excess of EE resulted in a 29% increase in $\dot{V}O_2$ and 56% increase in $\dot{V}CO_2$ (1). This corresponds to a 24% increase in EE associated with nutrient infusion. The patients in our study did not receive a large amount of dextrose (<300mg/day) or calories, and in only two patients did energy from nutrient infusion exceed or meet the measured total EE. Therefore, the large increase in resting EE above predicted EE we observed is unlikely due to nutrient infusion alone.

Varying degrees of severity of illness is likely a major factor responsible for differences in EE reported by various investigators. Unfortunately, few objective methods are available to evaluate and stratify different groups of critically ill patients. In an attempt to quantify the severity of illness of our patient population, two scoring systems were used. Each patient was scored using the APACHE II system (16) on admission to the ICU and the sepsis score (11) on the day of the study.

The APACHE II uses twelve basic physiological parameters, age and chronic disease to stratify acutely ill patients into prognostic mortality risk categories. Kresowick et al. recently used APACHE II as part of the stratification process to study the efficacy of nutritional support by looking at patient mortality (17). They found that in two groups of patients with similar APACHE II scores, 19 versus 22, the group of patients receiving adequate caloric intake had a significantly higher survival (73%) than a group who did not receive adequate caloric intake (46%). The mean APACHE II score for our patients was 23, which, according to Knaus's study of 5815 ICU admissions, places our patients in the top one-third of the scores, implying severe illness with poor prognosis.

Elebute and Stoner proposed the sepsis score to grade the severity of sepsis by numerically scoring such categories as local effects of infection, pyrexia, secondary effects of sepsis and laboratory data (11). Dionigi et al. using this sepsis score found that in their group of patients, a sepsis score of greater than 20 was associated with 18% survival (9). In our study, none of the 3 patients with sepsis scores greater than 20 survived. Patients

1, 3 and 10 who had the highest APACHE II scores and the highest percentage of resting EE above predicted EE (76.7±5.0%) also had an average sepsis score of 20±3.

The large increase in resting EE above predicted EE observed was probably attributable to the fact that the patients studied were severely ill. The significant correlation between individual APACHE II scores with percentage increase in resting above predicted EE suggests the APACHE II may be a valuable system to assist in stratifying critically ill patients for the purpose of evaluating nutritional studies. Similiarly, the addition of the sepsis scoring system may further enhance the descriptive process. Because of the small number of patients studied, the relationship between these scoring systems and EE requires further investigation.

Pain can have a considerable effect on overall EE. Weissman et al. observed a lower $\dot{V}O_2$ and $\dot{V}CO_2$ in one critically ill patient who was heavily sedated with narcotics when compared to no sedation (30). Rodriquez et al. (24) and Rouby et al. (25) have reported similar reductions in $\dot{V}O_2$, $\dot{V}CO_2$, and EE in groups of critically ill patients after they had received large amounts of analgesia. In our study, analgesia was administered on an "as necessary" ICU routine. As a result, following the metabolic response to analgesics was difficult as time of administration and amount given varied between patients. However, in two patients (patients 1 and 9), for which post-event resting EE was not significantly greater than resting EE, closer analysis of the data suggested that analgesia may be an important factor affecting EE. For both patients, examination of EE in relation to analgesia/sedation administration demonstrated that periods during which larger amounts of sedation were given were associated with a significant decrease ($p<0.05$) in EE. For example, cumulative resting EE (including both resting and post-event resting EE) for patient 1, during a 4 hour period in which the patient received the largest amount of analgesia/sedation (25 mg morphine, 10 mg diazepam) compared to resting EE in the remaining 20 hour period, decreased from 2858±205 kcal/day to 2537±96 kcal/day. This represented a 12.7% decrease in EE associated with the sedation/analgesia given. Similarly, the mean EE for all activities were significantly less ($p<0.05$) during the 4 hour period compared to those measured during the remaining 20 hours. Interestingly, it was also noted that the four hour period in which the patient was heavily sedated was the only period in which no state of agitation and restlessness was observed.

To further emphasize the importance of sedation on EE, for 8 of the 10 patients studied, an average of 3.3±1.9 hours of agitation and/or restlessness was observed during the 24 hour period. This represents a 15.0±8.2% contribution to the total EE for those patients. These data suggest that sedation can have a considerable effect on both resting and total EE of the critically ill patient.

Weissman et al. found that patients' EE after stimulation with chest physiotherapy or bathing, did not immediately return to baseline resting values (31). Although the patient may have appeared to be resting comfortably, it took up to 45 minutes for a true resting state to be re-established. Our measurement of a 5.8%

increase in post-event resting EE above EE taken following 30 minutes of rest is in agreement with this observation. The largest increase in EE above resting levels during various activities was associated with those activities requiring repositioning of the patient such as weighing the patient on a bed scale, administering chest physiotherapy, and performing a chest x-ray. From observation, it appeared that pain and discomfort experienced by the patient during repositioning may be major factors contributing to increased EE. Furthermore, it appeared that patients who received analgesics immediately prior to an activity had a lesser increase in EE associated with the activity. The effect of timing and dose of analgesic given may be partially responsible for the large variations in the percentage increase in EE above resting EE during various activities.

Weissman et al. observed about a 20% increase in $\dot{V}O_2$ and $\dot{V}CO_2$ above resting levels during activities such as physical examination, visitor attendance, bed bath and chest x-ray. We also observed an approximate 20% increase in $\dot{V}O_2$ and $\dot{V}CO_2$ for these activities (31).

Although these seemingly large increases in EE above resting EE were observed during various activities, contribution of the activities to total EE was relatively small. For all patients, total EE ranged from 1.4 to 10.6% with a mean total EE of 6.9±2.6% above the resting EE. Previous studies suggest that for ambulatory patients, daily activities can contribute from 0 to 40% of the resting EE and therefore a mean activity factor of 20% above resting

EE is appropriate (12,18). Results of the present study indicate this figure does not reflect actual additional energy needs for the mechanically ventilated critically ill patient. This is an important finding since excess nutrient infusion in critically ill patients may stress both cardiovascular and respiratory systems by increasing $\dot{V}O_2$ and $\dot{V}CO_2$ (1,2) and may result in fatty infiltration of the liver (20,27). From our data, it appears that an activity factor of 10% above the measured resting EE should adequately meet the EE associated with routine ICU activites.

V Conclusions

In conclusion, the ability to determine EE in critically ill patients using a portable metabolic cart represents a major advance in nutritional management:

1) Many factors such as sedation, feeding, time of measurement and degree of illness can have a significant effect on the results obtained. This is evident from the large variation observed in studies of critically ill patients that compare measured resting EE with predicted EE. Patients are extremely variable with regard to the degree of illness and therefore objective stratification is essential. Until patients can be accurately stratified by severity of illness, the use of derived equations to universally predict the EE of critically ill patients must be seriously questioned.

2) From observation, it appears that sedation may have a very important influence on resting EE, EE during activities and total EE.

3) It is evident from this study of 10 critically ill patients that, in order to avoid the undesirable complications of overfeeding, an activity factor of 10% above the actual measured resting EE to account for routine activities in the ICU is appropriate in estimating daily energy requirements.

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CHAPTER 4

THE EFFECT OF ROUTINE ADMINISTRATION OF ANALGESIA ON ENERGY EXPENDITURE IN CRITICALLY ILL PATIENTS

I Introduction

Administration of large amounts of analgesia, sedatives and paralytic agents have been shown to significantly decrease EE in mechanically ventilated critically ill patients. Rouby et al. (18) and Rodriquez et al. (16) found that $\dot{V}O_2$ decreased approximately 20% following administration of large doses (0.5 to 4mg/kg) of morphine to critically ill postsurgical patients. Clifton et al. found resting EE fell an average of 58% of the original level when mechanically ventilated neurosurgical patients were given a paralyzing dose of pancuronium bromide. However, most studies in which EE has been measured to determine the degree of hypermetabolism and/or for provision of nutritional support have not considered the amount of analgesia, sedative and paralytic agents given to patients. Recently Weissman et al. during an investigation of EE in critically ill patients observed that for one patient, both $\dot{V}O_2$ and $\dot{V}CO_2$ were lower when the patient was sedated compared with a nonsedated state (22). Results from 24 hour EE studies of critically ill patients reported in Chapter 3 support this finding. Administration of analgesia and/or sedatives was often accompanied by a decrease in EE. Routine administration of analgesia generally refers to analgesia given to patients "as necessary" (prn) (13). The amount and frequency of analgesia administered to patients is usually left to the discretion of the attending staff. For example, a commonly prescribed dose of analgesia might be 5-10mg of intravenous (IV) morphine given prn.

The effect of analgesia and sedation on EE in two patients studied during the previous 24 hour study (Chapter 3) is illustrated in Figures 4-1 and 4-2. A minute by minute account of EE is presented for a period of time prior to, during and following analgesia and/or sedation administration. The EE measurements for the first patient illustrated in Figure 4-1 were performed between 1235 hours and 1330 hours with the last dose of analgesia administered at 0800 hours (5mg morphine). At the beginning of the period, the patient appeared very agitated, restless and was moving his body and limbs without purpose; EE during this period of agitation was 3999±200 kcal/day (duration=19 minutes). In response to his apparent discomfort, the attending nurse administered 5mg of IV morphine followed 10 minutes later by administration of 5mg of IV diazepam. Post-sedation, the patient appeared more comfortable and rested quietly in bed; the EE during this period was 3070±91 kcal/day duration=25 minutes).

The EE measurements of the second patient illustrated in Figure 4-1 were performed between 0440 hours and 0530 hours; the last dose of analgesia was administered at 1950 hours during the previous evening (5mg morphine). At the beginning of the study period the patient appeared to be resting comfortably with his eyes closed (possibly sleeping); EE during this period was 2055±71 kcal/day (duration=21 minutes). At 0500 hours the patient was awakened and repositioned in bed; EE during repositioning was 2559±89

FIGURE 4-1

Effect of IV analgesia (morphine) and sedation (diazepam) administration on energy expenditure in a critically ill patient. Continuous measurement of energy expenditure was made between 1235 and 1330 hours.

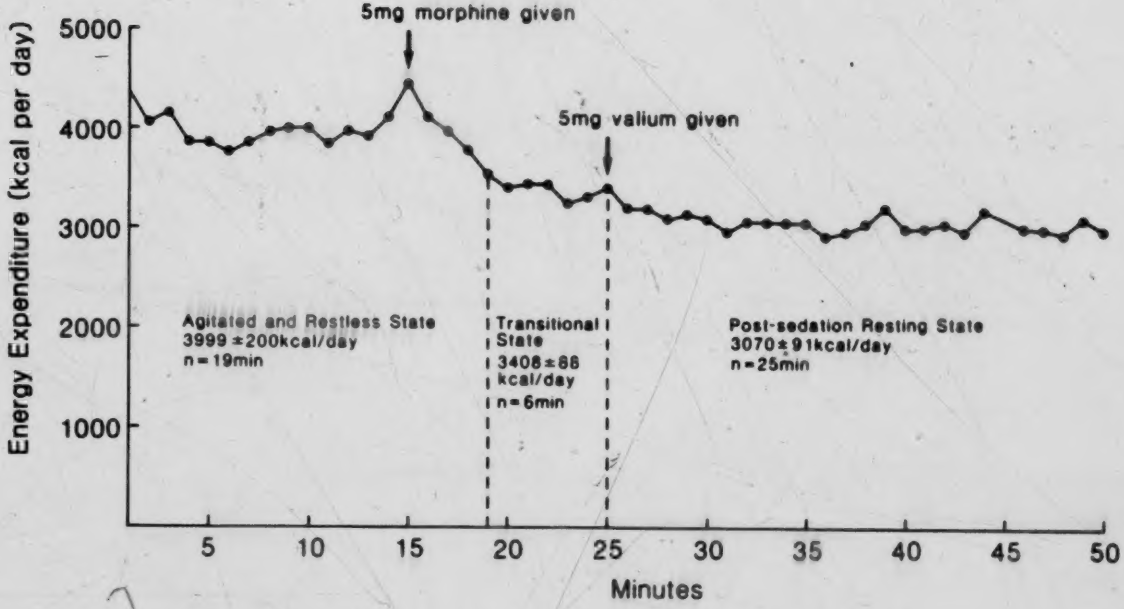
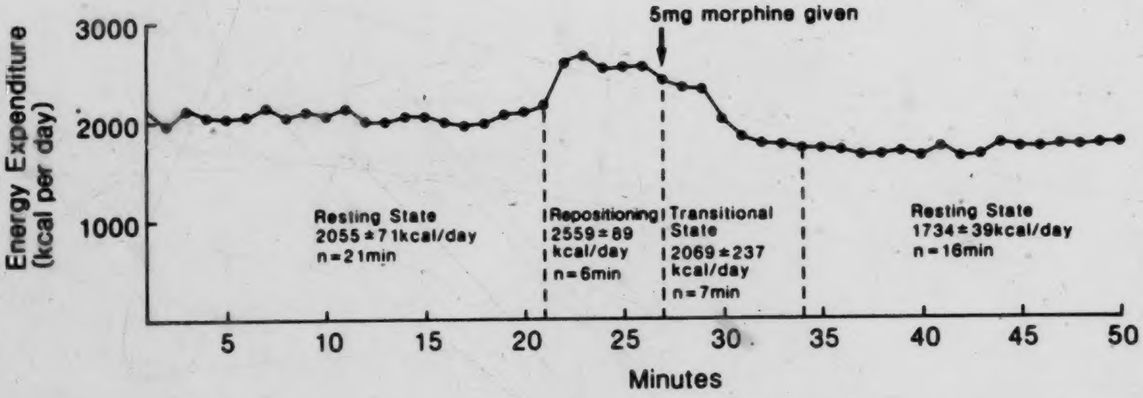


FIGURE 4-2

Effect of IV morphine administration on energy expenditure in a critically ill patient following the activity of repositioning the patient in bed. Continuous measurement of energy expenditure was made between 0440 and 0530 hours.



(duration=6 minutes). Following repositioning, the attending nurse administered 5mg of IV morphine to the patient. Postsedation the patient appeared to be resting comfortably; EE during this period was reduced to 1734±39 kcal/day (duration=16 minutes). The lower EE observed following repositioning compared to EE observed prior to repositioning was not expected as EE usually remains elevated for up to 30 minutes following an activity such as repositioning (22). It is therefore likely that the lower EE observed following repositioning can be attributed to the effect of morphine. The results discussed in Chapter 3 and the observations presented above strongly suggest that routine administration of analgesia and/or sedatives decreases EE in critically ill patients.

The primary purpose of this study was to determine the effect of routine IV analgesia administration on EE in critically ill patients during rest and various activities such as chest physiotherapy and chest x-ray. Additional objectives were: (i) to determine if the method of analgesia infusion, bolus IV injection versus continuous IV infusion, would affect EE differently; and, (ii) to compare measured resting EE with and without analgesia, to predicted EE based on the Harris and Benedict equation (7).

II Materials and Methods

(i) Patient Description

Seven patients (6 males, 1 female) admitted to the General Systems ICU at the University of Alberta Hospitals were studied. Age of the patients was 54±15 years (mean±SD). Clinical descriptions of the patients, APACHE II score on admission to the ICU, number of days patients were studied post-ICU admission, and outcome are presented in Table 4-1. The APACHE II score was used to define the clinical status of the patient upon admission to the ICU (10). All patients were intubated and mechanically ventilated in the assist/control mode, with a mean F_IO_2 of 0.33±0.06. Patients who were hemodynamically unstable and/or required constant analgesia for pain control were excluded from the study. The protocol was approved by the Ethics Committee of the University of Alberta Faculty of Medicine and the University Hospital and informed consent was obtained for all participants.

(ii) Energy Expenditure Measurements

The $\dot{V}O_2$ and $\dot{V}CO_2$ measurements were made using a Gould 9000IV Computerized Pulmonary Function Cart (Medical Products Division, Dayton, Ohio). The Gould 9000IV was validated prior to and at the end of each study as described in Chapter 3. The connection of the Gould 9000IV to the patient's ventilatory circuit for EE measurements was the same as described in Chapter 3.

(iii) Administration of Analgesia

Patients did not receive any analgesia or sedatives for at least four hours prior to starting the study. No analgesia was administered during the first half of the protocol, performed during the morning. A schematic diagram of the morphine protocol is presented in Figure 4-3. Period 1 refers to all measurements made when morphine was not administered and when designated by subscript b or c respectively refers to measurements made on the day bolus

TABLE 4-1

Clinical Description of Critically Ill Subjects

Patient	Sex	Age	Clinical Description*	Admission Days APACHE II Score	Day of Study Post-ICU Admission	Outcome**
1	M	68	Respiratory failure secondary to H. influenza pneumonia, emergency laparotomy for perforated duodenal ulcer, Pseudomonas septicemia	20	4,5	D
2	M	55	Gunshot wound to abdomen, extensive small bowel resection, total abdominal colectomy and ileostomy. Massive blood transfusion	16	4,5	S
3	M	75	Respiratory failure secondary to COPD and pneumonia, ischemic heart disease	27	4,5	D
4	M	31	MVA, flail chest, pulmonary contusion, laparotomy for repair of ruptured diaphragm and lacerated liver, facial smash, basal skull fracture	14	4,5	S

Continued on Page 142

(Continuation of TABLE 4-1)

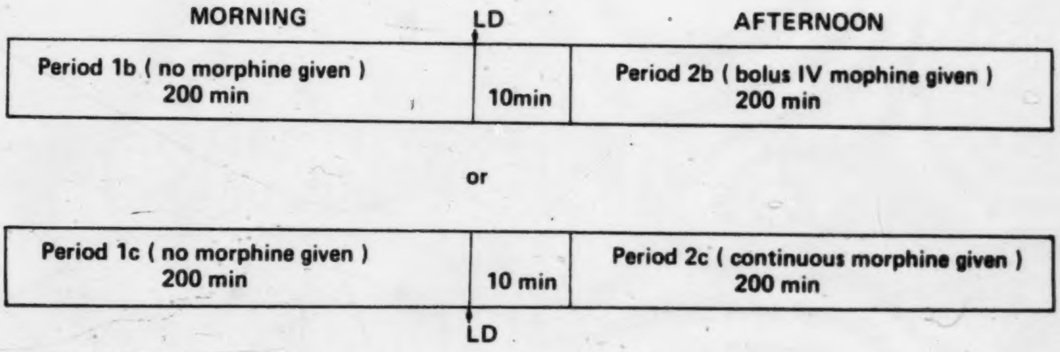
5	M	60	Acute necrotizing pancreatitis, laparotomy for drainage of intra-abdominal abscess and debridement of necrotic pancreatic tissue, staphylococcal septicemia	23	26,27	D
6	M	42	70% TBSA burn with respiratory and renal failure, Pseudomonas septicemia	21	22,23	D
7	F	48	Ankylosing spondylitis with severe restrictive pulmonary defect, Crohn's disease, laparotomy for small bowel resection, jejunostomy, ileostomy	20	21,22	D

* Post-op - postoperatively; COPD - chronic obstructive pulmonary disease; MVA - motor vehicle accident; TBSA - total body surface area

** D - deceased; S - survived

FIGURE 4-3

Diagram of the morphine protocol used. On day 1 and 2 during the morning study period, no morphine was administered to the patient. At the end of the series of rest, activities and postevent periods a loading dose (LD) of 0.15mg IV morphine/kg/body wt, followed by either the bolus IV injection morphine protocol (period 2b) or continuous IV morphine infusion (period 2c). Measurements for period 2 were not started until 10 minutes after the loading dose of morphine was given to the patient.


MORNING
LD
AFTERNOON
Period 1b (no morphine given)
200 min
10min
Period 2b (bolus IV mophine given)
200 min
or
Period 1c (no morphine given)
200 min
10 min
Period 2c (continuous morphine given)
200 min
LD

morphine injections (period 1b) and continuous morphine infusion (period 1c) were given. Period 2 refers to all measurements made during morphine administration and when designated by subscript b or c respectively refers to measurements made during bolus morphine injections (period 2b) and during continuous morphine infusion (period 2c).

Patients were allowed to rest quietly and no procedures or activities were performed for one hour prior to starting the study. The first resting EE measurement was made at approximately 0630 hours each day for a 1/2 hour period. Following the resting EE measurement, a series of activities routinely performed in the ICU were followed in a defined sequence and for a specific length of time. Each activity was followed by a 1/2 hour period (post-event period) during which time the patient was allowed to rest quietly with minimal disturbance by attending staff. Energy expenditure was measured continuously during rest, activities and post-event periods. Sequence of activities and their average duration are presented in Table 4-2. Two patients did not have dressing changes, the substituted activity was patient weighing on a sling-type bed scale.

Following EE measurement of the last post-event period, patients were randomly assigned to receive either bolus intravenous morphine injections (period 2b) or continuous IV morphine infusion (period 2c) (Figure 4-3). A loading dose of 0.15 mg of morphine sulfate per kilogram body weight per hour (mg/kg/hr) was administered IV to the patient at the beginning of both morphine protocols. Measurement of

TABLE 4-2

Sequence of Rest, Activities, and Post-Event Periods Performed During Periods 1 and 2

	Activities	Duration (Minutes)
(1)	Rest	30
(2)	Chest X-ray	5
(3)	Post-Event Period	30
(4)	Nursing Assessment	15
(5)	Post-Event Period	30
(6)	Chest Physiotherapy	10
(7)	Post-Event Period	30
(8)	Dressing Change (or weighing of bed scale)	20
(9)	Post-Event Period	30
	Total	200

(150 minutes of rest, 50 minutes of act[illegible]ties)

EE commenced 10 minutes following the inital dose of morphine was given (14). The EE was measured for 1/2 hour while the patient rested undisturbed, this was considered to be resting EE for period 2. The initial dose of morphine was followed by either bolus morphine injections of 0.10mg/kg given every two hours or by continuous morphine infusion of 0.05mg/kg/hr. Morphine administration continued until the complete sequence of rest, activities and post-events was completed. Sequence and duration of all rest, activities and postevent periods was repeated as closely as possible to those performed earlier during period 1.

The order of period 1 and 2 was not randomized. It was felt that a carry-over effect could influence EE if analgesia was given during the first portion of the protocol. Therefore studies performed in the unsedated state (period 1) were performed in the morning and always preceded studies performed in the sedated state (period 2) which were performed in the afternoon.

(iv) Definitions

Non-activity EE refers to EE during the post-event periods (four 30 minute periods for each patient) and resting EE (one 30 minute period for each patient). Total EE refers to cumulative energy expended during all rest, activities and post-event periods. Total EE was calculated for periods 1 and 2 on both days of study. The value for total EE was obtained by dividing mean EE (measured in kcal/day) of each rest, activity and post-event period by 1440 to convert EE to kcal/minute, and then multiplying these values by their corresponding mean duration (measured in minutes).

The ability of analgesia to blunt the rise in EE associated with chest x-ray and chest physiotherapy was determined by comparing the percent rise in EE during periods 1 (no morphine) and 2 (during morphine administration). The percent rise in EE associated with chest x-ray was calculated from the EE during performance of the procedure divided by the EE of the preceding rest period and for chest physiotherapy, from the EE during chest physiotherapy divided by the EE of the preceding post-event period.

(v) Statistical Analysis

A Student's t-test for paired data was used to determine differences between resting EE, non-activity EE, total EE and percent rise in EE associated with chest x-ray and chest physiotherapy between periods 1 and 2. A paired t-test was also used to compare differences between periods 1c and 2c and periods 1b and 2b. For the nonactivity period, a paired t-test was used to determine differences between periods 1 and 2 for $\dot{V}O_2$, $\dot{V}CO_2$, respiratory quotient (RQ) and minute ventilation ($\dot{V}_E$) for all patients and for each patient on an individual basis (20). Pearson's correlation coefficient was used to evaluate the relationship between admission APACHE II score and percentage that resting EE, for periods 1 and 2 was above predicted EE (10). All data is expressed as the mean±SD and a probability level of less than 0.05 was accepted for statistical significance.

(vi) Nutritional Support

Four patients received parenteral nutrition, 2 patients received enteral nutrition and 1 patient received only intravenous dextrose during the study period. Infusion rates and type of nutrient solutions received by patients were kept constant for the 24 hour period preceding and during the entire study period. Mean caloric intake was 1761±920 kcal/day (range = 264 to 2625 kcal/day).

(vii) Predicted Energy Expenditure

Predicted EE was determined using the Harris and Benedict equation (7):

$$\text{male EE} = 66.47 + 13.75W + 5.0H - 6.76A$$

$$\text{female EE} = 655.10 + 9.56W + 1.85H - 4.68A;$$

where: EE = energy expenditure in kcal/day; W = weight in kilograms;
H = height in centimeters; A = age in years.

A pilot study was performed on one patient to validate the protocol and to ensure that periods 1 and 2 were repeated in a reproducible fashion. One nurse was responsible for the care of a given patient during the entire day of study.

III Results

Admission APACHE II score of the patients was 20±4, and 5 of the 7 patients died during the post-study ICU course indicating that the population studied was severely ill (Table 4-1). Mean amount of morphine received by patients as a loading dose was 11.3±2.5mg and the mean amount received during the remainder of the study period was 14.2±5.5mg. No significant correlation was found between the patient's admission APACHE II score and degree to which measured resting EE exceeded predicted EE for period 1 (r=0.59, p=0.08) or period 2 (r=-0.50, p=0.13).

Predicted EE, resting EE and the degree to which resting EE exceeded predicted EE for both period 1 (no analgesia) and period 2 (during analgesia) are presented in Table 4-3. Predicted EE was 1604±247 kcal/day. Resting EE during period 1 was significantly higher than resting EE during period 2 (2200±563 kcal/day vs 2067±538 kcal/day, $p<0.01$). This corresponded to a 36.8±17.4% and 27.9±17.2% increase in measured resting EE above predicted EE for periods 1 and 2 respectively ($p<0.01$).

The results for comparisons of nonactivity EE (resting EE and EE during postevent periods) for periods 1 and 2 (no morphine vs IV morphine), periods 1b and 2b (no morphine vs bolus IV morphine injections) and periods 1c vs 2c (no morphine vs continuous IV morphine) are presented in Table 4-4. Overall mean EE during the nonactivity period was greater for period 1 than 2 (2209±536 kcal/day vs 2041±522 kcal/day, $p<0.01$), period 1b than 2b (2190±499 kcal/day vs 2039±484 kcal/day, $p<0.01$) and period 1c than 2c (2227±586 kcal/day vs 2042±574 kcal/day, $p<0.01$). For individual patients EE was greater during period 1 than period 2 for all 7 patients, however for 2 patients the difference was not statistically significant. For both period 1b compared to period 2b and period 1c compared to 2c, EE of individual patients was higher during period 1 than period 2. However, for both types of morphine infusion, the difference was not statistically significant for 3 patients.

Nonactivity $\dot{V}O_2$ and $\dot{V}CO_2$ followed a response similiar to EE measurements made with and without morphine. Oxygen consumption was significantly higher during period 1 than period 2 (367±16ml/min vs

TABLE 4-3

Predicted and Resting Energy Expenditure of Patients, With and Without Morphine Administration (mean ± SD)

Patient	kcal/day			% Resting EE was Above Predicted EE for Period 1* (no morphine)	% Resting EE was Above Predicted EE for Period** (during morphine administration)
	Predicted	Resting EE During Period 1* (no morphine)	Resting EE During Period 2** (during morphine) administration)		
1	1582	1808	1640	14.3	3.7
2	1891	2928	2777	54.8	46.9
3	1538	1878	1660	22.1	10.8
4	1711	2622	2482	53.2	45.1
5	1715	2611	2368	52.2	38.1
6	1684	2360	2241	40.1	33.1
7	1104	1336	1300	21.0	17.8
	1604±247	2220±563	2067±538	36.8±17.4	27.9±17.2

* Period 1 = period 1b + period 1c

** Period 2 = period 2b + period 2c

TABLE 4-4

Non-Activity EE of Patients During Periods 1 and 2 (mean ± SD)

Patient	(kcal/day) Period 1	Period 2	Period 1b	Period 2b	Period 1c	Period 2c
1	1827±152	1528±130**	1929±55	1577±151*	1725±151	1479± 94*
2	2882±395	2732±273 NS	2684±481	2525±219 NS	3079±147	2939±116 NS
3	1901± 95	1794±165 NS	1875±62	1789±239 NS	1927±120	1798± 64 NS
4	2666±186	2420±150*	2614±85	2518±118*	2719±253	2322±114*
5	2525±112	2359± 74**	2570±90	2381±49**	2479±84	2336±93*
6	2297±70	2171±86***	2330±32	2175±103*	2265± 86	2167± 84*
7	1364± 51	1284± 77*	1331± 15	1311± 63 NS	1398± 54	1256± 87*

* $p<0.05$; ** $p<0.001$; *** $p<0.001$, NS - not significant

Period 1 - measurements made on day 1 and 2 without morphine administration;
Period 2 - measurements made on day 1 and 2 during morphine administration (including bolus and continuous morphine);
Period 1b - measurements made without morphine on day that bolus morphine injections given;
Period 2b - measurements made during bolus morphine injections;
Period 1c - measurements made without morphine on day that continuous morphine infusion was given;
Period 2c - measurements made during continuous morphine infusion

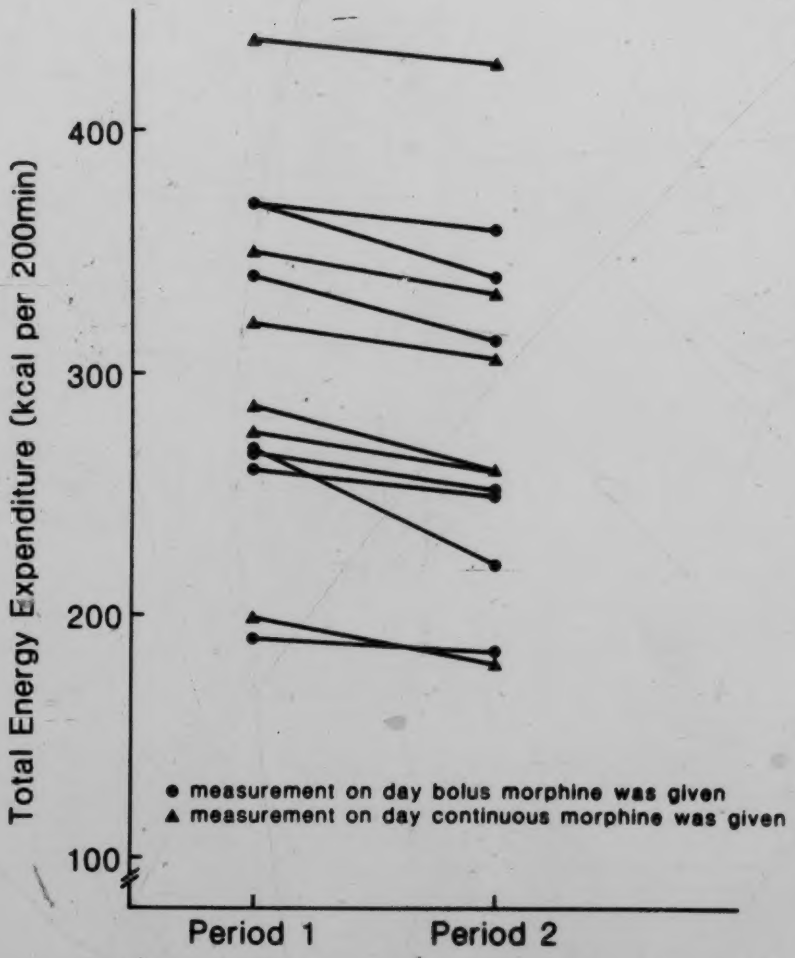
338±7ml/min, $p<0.01$). Carbon dioxide production was also significantly higher during period 1 than period 2 (340±20ml/min vs 305±9ml/min, $p<0.05$). For individual patients $\dot{V}O_2$ and $\dot{V}CO_2$ during the nonactivity period were significantly higher during period 1 than period 2 for 5 of the 7 patients ($p<0.05$). The mean RQ during the nonactivity period without morphine (period 1) was .93±.04 and following morphine (period 2) the RQ was .90±.02, this difference was not statistically significant. The patient's $\dot{V}_E$ during period 1 was significantly greater than $\dot{V}_E$ during period 2 (10.7±0.8L/min vs 9.5±0.4L/min, $p<0.05$).

Total EE measured for a mean duration of 200 minutes was 315±77kcal for period 1 and 290±77kcal for period 2. This represented a significant decrease of 8.6±9.8% in EE associated with morphine administration ($p<0.01$). Total EE was higher during period 1b than 2b (307±77kcal vs 291±77kcal, $p<0.05$) and also higher during period 1c than 2c (320±82 vs 290±84, $p=0.05$). The fall in total EE associated with morphine administration is illustrated in Figure 4-4.

For periods 1 and 2, percent rise in EE associated with chest x-ray was 15.7±8.7% and 21.2±14.4% and for chest physiotherapy was 19.6±10.9% and 22.8±11.5% for periods 1 and 2, respectively. For period 1b and 2b, percent rise in EE associated with chest x-ray was 15.4±10.0% and 20.9±8.6% and for chest physiotherapy was 21.9±13.3% and 24.0±11.1%, respectively. For periods 1c and 2c, percent rise in EE associated with chest x-ray was 16.0±8.0% and 21.4±19.3% and for chest physiotherapy was 17.2±8.3% and 21.5±12.5%, respectively. Percent rise in EE associated with chest x-ray or chest physiotherapy

FIGURE 4-4

Fall in total energy expenditure (200 minutes) associated with morphine administration for the 7 critically ill patients studied. Period 1 refers to total energy expenditure when no morphine was given and period 2 refers to total energy expenditure when IV morphine was administered to the patient.



was not significantly different for periods 1 and 2, periods 1b and 2b or periods 1c and 2c.

IV DISCUSSION

As discussed in Chapter 3, many reports have attempted to determine the degree of hypermetabolism associated with critical illness. However, based on the present available data, there appears to be little consensus among investigators. Several researchers have reported critically ill patients to be only modestly hypermetabolic. Baker et al. found a mean increase in EE of 4.6% above predicted normal levels for a group of mechanically ventilated ICU patients (2). Similarly, Weissman et al. found mean resting EE to be 3.8% above predicted normal levels for a group of mechanically ventilated postsurgical ICU patients (23). Mann et al. reported a mean increase in EE of 15% above predicted normal levels for 50 acutely ill patients (12).

In constrast to these reports, other investigators have reported large increases in EE associated with critical illness. Savino et al. reported mean resting EE to be 28% above normal for postpolytrauma and postoperative surgical patients who were receiving mechanical ventilation in the assist-control mode and 43.7% above normal when the same patients were studied while receiving intermittent mandatory ventilation (19). Wynn et al. reported a mean increase in EE of 40% above normal levels for 28 postoperative critically ill patients (24). During our study of 24 hour EE in 10 mechancially ventilated patients (APACHE II score = 23±7) mean resting EE was 47% above predicted normal levels based on the Harris and Benedict equation (20). For the 7 patients presented in this study (APACHE II score = 20±4), mean resting EE was 37% above predicted normal levels when no morphine was administered and 28% above predicted normal values when routine amounts (0.05mg/kg/hr) of morphine were administered.

Several factors likely contribute to this large reported variability in EE seen in critically ill patients. Factors such as previous nutritional status of the patient (1,11) infusion of nutrients (1,8,15,17,25), anxiety and pain (5,22), mode of ventilatory support (19) and severity of illness (20,23) can affect EE of critically ill patients. Although the effects of administering very large amounts of morphine to critically ill patients has been studied, the effects of routine amounts of analgesia commonly administered to ICU patients, has not been previously reported.

Rouby et al measured the metabolic response to injection of 0.5mg/kg of morphine (e.g. 35mg of morphine for a 70kg man in 24 mechanically ventilated patients) (18). They found the degree and duration of sedation varied markedly among patients. In their study, for 10 patients, the initial $\dot{V}O_2$ was elevated and morphine administration resulted in a significant decrease in $\dot{V}O_2$ of 21%. For the remaining 14 patients, initial $\dot{V}O_2$ was normal and morphine administration still resulted in a significant decrease in $\dot{V}O_2$ but of a lesser degree (9% decrease).

Rodriquez et al. compared the effects of morphine administered to a group of postoperative patients who underwent intraabdominal or intrathoracic procedures (16). Eight patients received a mean amount of 0.62mg/kg of morphine and 10 patients received a larger dose with a mean amount of 4.5mg/kg of morphine. Oxygen consumption and EE were significantly lower for patients who received the larger morphine dose compared to patients who received the lesser dose ($\dot{V}O_2$ was 65ml/kg/hr vs 170ml/kg/hr and EE was 60kcal/hr vs 140kcal/hr, respectively).

Taylor et al. observed a 29% decrease in EE from the original level in 5 burn patients following administration of morphine at a rate of 0.30mg/kg/hr (21). Our results support these findings. In our study, even though a considerably smaller dose of morphine (0.05mg/kg/hr) was administered to patients, EE during rest, nonactivity periods and total EE decreased approximately 8% compared to EE measurements made when morphine was not administered. This response in EE appeared to be similiar for bolus injections and continuous infusion of morphine.

The effect of analgesia on EE was highly variable among patients. Reduction in resting EE following bolus morphine injections ranged from 4.5% to 20.2% and following continuous morphine infusion ranged from 1.0% to 10.6%. Similarly the reduction in nonactivity EE following bolus morphine injections ranged from 1.5% to 18.2% and following continuous morphine infusion ranged from 4.3% to 14.6%. The reason for the large variability seen among patients is not precisely known, but could be related to several factors. The degree of pain experienced by a mechanically ventilated patient is often difficult to assess (3). All patients included in this study were critically ill, however severity and type of illness of individual patients was variable (Table 4-1). It is therefore likely that degree of pain and discomfort experienced by individual patients was also variable. Administration of morphine at a defined amount and rate may have been sufficient to control pain and discomfort in some patients but not in other patients. A second factor that may contribute to the variable degree of response in EE associated with morphine administration was the variable amount of analgesia and/or sedative which patients had received on days prior to the study. Tolerance can develop after repeated administration of morphine, with the analgesic effect being lessened (24). On the other hand, repeated use of analgesic drugs can be cumulative in their action (3). Despite cessation of analgesia and/or sedative administration 4 hours prior to study, it is possible that a carry-over effect may have influenced EE of some patients during period 1.

Although routine amounts of analgesia did not appear to blunt the increase in EE associated with specific activities such as chest x-rays or chest physiotherapy, total EE (including rest, postevent periods and activities) was significantly decreased during the period morphine was administered compared to the period when morphine was not given. In Chapter 3, nonambulatory mechanically ventilated critically ill patients spent approximately 75% of the time in a 24 hour period in a non-active or resting state with daily activities accounting for approximately 25% of the time during a 24 hour period. Since both non-activity EE and resting EE were significantly decreased during morphine administration, it is not surprising that total EE was also decreased.

A possible explanation for the decrease in EE and $\dot{V}O_2$ seen following IV morphine administration is a reduction in cardiac output which resulted in a decreased delivery of oxygen to the tissue. Although cardiac output was not measured in this study, Rouby et al. found that cardiac output and oxygen delivery were significantly decreased following IV administration of large doses of morphine to critically ill patients (18). However, they found that arterial-venous oxygen difference did not change therefore suggesting that decreased $\dot{V}O_2$ was not due to a low oxygen delivery but rather due to a primary effect of morphine on decreasing oxygen consumption of the tissues. Regardless of the mechanism, this finding has important implications with respect to measurement of the degree of hypermetabolism associated with critical illness. These results suggest that it may be possible to alter the EE, and possibly the degree of hypermetabolism, associated with critical illness by manipulating the amount and type of sedation given to patients. Finally and most importantly, the large variability in EE associated with critical illness reported by other investigators may in part be due to varying regimens used to sedate ventilated patients.

In the previous study (Chapter 3), the degree to which resting EE exceeded predicted normal levels was significantly correlated to the admission APACHE II scores of the patients. This suggested that the APACHE II score, used to quantify the severity of illness, could be related to the degree of hypermetabolism exhibited by the patient.

For the 7 patients in this study, the APACHE II score on admission to the ICU was not significantly correlated to the degree to which resting EE exceeded predicted EE, for either periods 1 or 2. In fact, the degree of hypermetabolism as assessed by the degree to which resting EE exceeded predicted EE levels was significantly greater when morphine was not given to patients compared to when morphine was administered. It appears that the degree to which measured EE exceeds predicted EE can be altered by morphine administration. The degree to which measured EE was altered was variable among patients. Alteration of measured EE was independent of the patient's admission APACHE II score. Therefore, the results of this study do not support the previous finding (Chapter 3) that the APACHE II score may be a useful predictor of degree of hypermetabolism associated with critical illness.

V Conclusion

Administration of a small dose of morphine (0.10mg/kg) significantly decreased EE in critically ill patients at rest and during nonactivity periods. Analgesia administered at this dose did not blunt the rise in EE associated with activities such as chest x-ray and chest physiotherapy. The method of analgesia administration, bolus injections or continuous infusion, appeared to have a similar effect on EE. It is concluded that administration of routine amounts of analgesia significantly lowers EE in mechanically ventilated critically ill patients.

VI References

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CHAPTER 5

DISCUSSION AND CONCLUSIONS

The development of portable automated systems capable of measuring gas exchange in critically ill patients to indirectly determine energy requirements is a significant advance. In the past, energy requirements of mechanically ventilated critically ill patients have been estimated using predictive formulas such as the Harris and Benedict equations (5) and the Aub and DuBois surface area formulas (1) with the addition of arbitrary factors to account for activity and the stress of illness. Several recent studies in which portable automated systems have been used to determine EE strongly support two important findings. Firstly, predictive formulas cannot accurately predict the measured EE of mechanically ventilated critically ill patients (2,3,7,12). Secondly, there is wide variation in the measured EE of groups of critically ill patients studied (2,3,7,9,12). Both of these findings support the need to accurately measure EE of a critically ill patient on an individual patient basis in order to provide the appropriate daily caloric needs of the patient and to study the efficacy of nutritional support.

We recently purchased an automated portable system at the University of Alberta Hospitals to study EE in mechanically ventilated critically ill patients. The purpose of the study described in Chapter 2 was to validate the Gould 9000IV Computerized Pulmonary Function Cart to establish its accuracy and any limitations of the system. During the initial in vitro studies large errors in $\dot{V}O_2$ measurements of approximately 43% when the system was tested at an F_IO_2 of 0.60 were found. This error was attributed to a leak in the Gould 9000IV spirometer. When the spirometer dumped the expired air, room air (F_IO_2=0.21) was entrained into the spirometer therefore diluting the expired air sample. This error was of small consequence to $\dot{V}CO_2$ measurements, however it was of significant consequence to $\dot{V}O_2$ measurements, especially at high F_IO_2 levels. We therefore modified the system was therefore modified by adding a large household dryer hose to the expired dump port of the spirometer. This provided an adequate amount of dead space to prevent entrainment of room air into the spirometer. The Gould 9000IV modified by the dryer hose was used for all measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ at all F_IO_2 levels and ventilator settings. Subsequently, the accuracy of $\dot{V}O_2$ measurements made at F_IO_2 values of 0.22, 0.40, 0.60 and 0.80 were +2.6±0.3%, +3.5±0.4%, +5.9±0.5%, and +16.9±0.6%, respectively. The fact that actual $\dot{V}O_2$ measurements always overestimated calculated $\dot{V}O_2$ and that this error was not random in nature suggested that a small leak in the system was still present. The accuracy of $\dot{V}CO_2$ measurements made at all four F_IO_2 levels was ±2.6%. From the results of this *in vitro* it was concluded that the Gould 9000IV with the dryer hose adaption can be used to accurately measure $\dot{V}O_2$ and $\dot{V}CO_2$ in mechanically ventilated critically ill patients who receive a F_IO_2 of 0.60 or less.

Nutrition research studies usually base the total daily caloric intake that patients receive on the total daily EE. The question then arises as to what is the total daily EE in the mechanically ventilated critically ill patient? Since it is not possible to measure 24 hour EE in all critically ill subjects on a continuous basis it was therefore necessary to study a group of critically ill patients to determine an appropriate factor to account for daily ICU activities. Weissman et al. recently reported 24 hour EE in 3 mechanically ventilated ICU patients and found daily EE exceeded resting EE by only 5% (11). Because the number of patients they studied was small and because the "ICU routine" may vary at different institutions, it was felt to be necessary to further investigate 24 hour EE in critically ill patients.

Ten mechanically ventilated General Systems ICU patients were studied. Various routine ICU activities such as repositioning the patient, chest physiotherapy, weighing the patient on a sling-type bedscale and chest x-ray were associated with large increases in EE above resting levels of 31±11%, 20±10%, 36±12% and 22±16%, respectively. However, because these activities were performed for relatively short durations during a 24 hour period, their total contribution to total daily EE was small. For repositioning the patient, chest physiotherapy, weighing the patient on a sling-type bed scale and chest x-ray, the overall contribution of these activites to total EE was approximately 5%.

Total EE of the 10 patients was only 6.9±2.6% above the resting level and ranged from 1.4% to 10.6% for individual patients. This result supports the conclusion that an activity factor of no greater than 10% is appropriate to apply to measured resting EE to account for total daily EE in mechanically ventilated critically ill patients.

An interesting observation made during the 24 hour patient studies was that the administration of analgesia and/or sedation was often associated with a reduction in EE. This was an important finding as it potentially meant that resting EE, total EE and EE during ICU activities in critically ill patients may be altered by administration of routine amounts of analgesia and/or sedatives. Although it has been previously shown that administration of large amounts of morphine to critically ill patients can significantly reduce EE by approximately 20% (8,9), the effects of small routine doses of analgesia commonly administered to ICU patients had not been reported. The purpose of the study described in Chapter 4 was therefore to study the effect of routine administration of analgesia (0.10mg morphine/kg body weight) on EE in mechanically ventilated critically ill patients.

The effect of administration of routine amounts of IV morphine, given as bolus injection and continuous infusion, on EE was studied in 7 mechanically ventilated General Systems ICU patients. Administration of either bolus IV injections or continuous IV infusion of morphine resulted in a significant reduction in EE compared to when no morphine was given. Resting EE, total EE measured for a 200 minute period, and nonactivity EE (defined as EE during rest and postevent periods) decreased by approximately 8% when morphine was administered compared to when no morphine was given. These results support the conclusion that routine administration of IV morphine significantly decreases EE in mechanically ventilated critically ill patients.

The reduction in EE found following IV morphine administration might be explained by a decrease in oxygen delivery to the tissues caused by a reduction in cardiac output. Although cardiac output was not measured, Rouby et al. found a significant reduction in both cardiac output and oxygen delivery following administration of large doses of morphine to critically ill patients (9). However, they found that arterial-venous oxygen difference did not change thus suggesting that EE did not decrease secondary to low oxygen delivery but rather to a primary effect of morphine on decreasing the tissue demands for oxygen. This finding has important research and clinical implications. With respect to previous research studies, it suggests that differences in EE of critically ill patients reported by investigators may be largely related to different analgesia regimens used at the various institutions to sedate mechanically ventilated patients. Taken one step further, the results of this study suggest that an "optimal" amount of analgesia and/or sedation given to patients may beneficially reduce their EE or degree of so called "hypermetabolism" thus making appropriate daily nutritional support easier to achieve.

The last question addressed by the studies reported in this thesis was the degree of hypermetabolism associated with critical illness. In both Chapters 3 and 4, the degree to which measured EE exceeded predicted EE (based on the Harris and Benedict equation) was determined. Measured resting EE exceeded predicted EE by 47±22% for the 10 patients studied during the 24 hour EE study (Chapter 3) and measured resting EE exceeded predicted EE by 28±17% for the 7 patients studied during IV morphine administration and 37±17% when IV morphine was not administered during the morphine study (Chapter 4). In both studies the increase in measured EE above predicted EE that was observed for all patients was considerably larger than most recent investigators have reported. The reason for this discrepancy is likely related to several factors, the major one being severity of illness. Based on our data and that of previous research studies it appears unlikely that the degree of illness is similar between individual patients and therefore the degree of hypermetabolism observed is likely to differ between patients. When extrapolated to patient series, it is not surprising that profound differences in results are observed. The degree to which resting EE exceeded predicted normal EE in critically ill patients ranged from -46 to 123% in Baker et al.'s study (2), from 14 to 133% in Gazzaniga et al.'s study (4), 23 to 83% in the study on 24 hour EE (Chapter 3) and 4 to 55% in the study on the effects of morphine on EE (Chapter 4).

An attempt was made to clarify the relationship between severity of illness and the degree of hypermetabolism seen in critically ill patients. All individual patients studied in Chapters 3 and 4 were scored on admission to the ICU using the APACHE II scoring system (6). It was hypothesized that patients with higher APACHE II scores were indicative of the more severely ill and they therefore would be expected to exhibit a larger increase in metabolic rate above predicted normal levels than patient with lower APACHE II scores. Therefore the APACHE II score determined on the day of ICU admission was correlated to the degree of hypermetabolism which was defined as the degree to which measured resting EE exceeded predicted EE. For the patients studied in Chapter 3 (24 hour EE studied), a significant correlation was found between the patient's admission APACHE II score and the degree to which measured resting EE exceeded predicted EE ($r=0.64, p<0.02$). However for patients studied in Chapter 4 (morphine study), no significant correlation was found between the patient's admission APACHE II score and either degree to which resting EE exceeded predicted EE during the period when no morphine was administered ($r=0.59, p=0.08$) or degree to which resting EE exceeded predicted EE during the period when morphine was administered ($r=-0.50$, $p=0.13$). The APACHE II score determined when the patient is admitted to the ICU is a static score that remains unchanged regardless of subsequent changes in the patient's clinical condition. Therefore it would be expected that the particular length of time between when the patient is admitted to the ICU and when EE measurements are made will influence this relationship. For example, the degree of hypermetabolism seen for a young healthy patient sustaining multiple injuries from a motor vehicle accident may be very high during the first days in the ICU, however following this initial rise the patient's EE would most likely decrease. However, the admission APACHE II score will remain the same for this patient and the degree to which resting EE exceeds predicted EE will change depending on the time at which the patient is studied.

In the morphine study, the degree to which measured EE exceeded predicted EE was reduced when morphine was administered compared to when morphine was not administered, however the patient's admission

APACHE II score remained the same. For the period when morphine was not given, a positive correlation was observed between the patient's admission APACHE II score and the degree to which measured resting EE exceeded predicted EE. However for the period when morphine was administered, a negative correlation was observed between the patient's admission APACHE II score and the degree to which measured resting EE exceeded predicted EE. This was not an expected finding and may possibly be explained by the fact that the administration of morphine resulted in variable reductions in resting EE among patients. It appears that larger reductions in EE occurred following morphine administration in patients who had higher admission APACHE II scores. These results suggest that it is unlikely that admission APACHE II score is a reliable predictor of degree of hypermetabolism seen in critically ill patients.

The results of EE measurements made in Chapter 3 and 4 strongly support the general conclusion that EE is extremely variable among mechancially ventilated critically ill patient. Presently there appears to be no method to accufately predict EE in this group of patients. Nutritional management based on predictive formulas may lead to inadequate or excess caloric intakes. Measurements of resting EE in individual patients by automated portable systems and the addition of a 10% factor to account for daily activity is the most accurate method to assess daily energy requirements of mechancially ventilated critically ill patients.

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